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ACIDOSIS IN CHILDREN, WITH REFERENCE TO THE PATHOLOGIC ANATOMY *

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CHICAGO

In the last decade pediatricians have come to recognize a form of acid intoxication occurring in children as a distinct clinical entity, the so-called acidosis.

This type is described by Abt[1] as occurring in robust children who have been previously healthy. Following a period in which the child's weight remains stationary and in which dissatisfaction with the food is shown, the disease becomes manifested by diarrhea, vomiting and a febrile reaction lasting a few days, after which there occur abdominal distention, and pronounced dyspnea characterized by rapid, labored respiration of wide amplitude; the liver becomes palpable, with firm round edges, the urine contains albumin, casts and the acetone bodies; in a few days the child passes into coma which is apt to terminate fatally. On postmortem examination the liver and kidneys are found to have undergone fatty changes. Abt also enumerates a variety of clinical conditions in which the acetone bodies are found, but in which diseases their occurrence is regarded merely as a symptom of the disease. In acidosis, the striking feature is the rapid abrupt clinical course in children who previously have been healthy. Parke[2] states that in several of his patients criminal poisoning was suspected, as in the case to be described.

This paper is concerned with the record of the clinical course and necropsy in a case which we believe to be one of acidosis, and an attempt to correlate the anatomic alterations with the clinical diagnosis.

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* Submitted for publication Nov. 25, 1916.

* Read before the Michael Reese Clinical Society, Dec. 6, 1915.

* From the Sarah Morris Hospital for Children and Department of Pathology, Michael Reese Hospital.

1. Abt: Am. Jour. Med. Sc., 1914, **147,** 86.

2. Parke: Jour. Am. Med. Assn., 1907, **49,** 1827.

REPORT OF CASE

History.—The patient, a male child aged 16 months, was brought to the Sarah Morris Hospital for Children, Aug. 3, 1915, because of vomiting. The history was that of a normal, robust child, who had been born spontaneously after a normal pregnancy, sat up at 5 months, cut his first tooth at 13 months and began to walk at 14 months; he was breast fed and was apparently in normal condition up to two weeks previous to his entry to the hospital, when he vomited after feeding. Because of this the mother started to wean him, substituting skimmed milk and a proprietary food, but the vomiting continued. The vomitus was dark-brown in color, of thick consistence, but contained no curds or blood. The urine decreased in amount, became dark-brown in color and had an offensive odor. August 1, the mother noticed that the ankles were swollen.

Examination and Course.—On admittance the child was in a drowsy, somnolent state and would shriek at times. The fontanels were closed, there was no tenderness about the head, the face was edematous; the ears were normal; there was strabismus of the right eye, and the pupils reacted to light; the nose was normal; the upper and lower incisors were present; the tongue was coated. The chest was symmetrical, expansion good, resonance normal; the breath sounds were vesicular and a few moist râles were heard posteriorly over both apices. The heart boundaries were normal, the sounds were clear and distinct; the abdomen was distended, the liver was palpable, the extremities were markedly edematous. The temperature was 100 F., the respirations 36 and the pulse 160. Shortly after admittance the child was placed in a mustard pack, stimulants were given hypodermically, and cathartics and alkalies by mouth. In the afternoon the temperature was 104.4 F., the pulse 154, respirations 46. Two-thirds milk with dextromaltose was given, which the child vomited. The following day the child's condition was worse; he refused food, moaned and screamed as if in pain, and only a small amount of urine was passed. The treatment of the previous day was repeated. The respirations became labored and gasping, the temperature, pulse and respiratory rate remained much the same, and he became comatose. The urine was cloudy, dark-amber in color, acid in reaction, contained albumin, acetone and fatty casts, also erythrocytes, leukocytes and fat globules. The blood showed 80 per cent. hemoglobin, 4,200,000 erythrocytes per cubic millimeter, and 10,200 white cells; the differential cell count was normal. The child died forty hours after admittance.

Necropsy.—Anatomic Diagnosis: Lipemia; lipuria; anasarca; marked fatty changes in the liver; marked fatty degeneration of the kidneys; cloudy swelling of the myocardium; passive congestion of the lungs; small accessory spleen.

The body was that of a white, well-nourished male infant weighing 19 pounds 13 ounces. There was present a general anasarca. The tissues of the limbs, body and head were edematous and pitted on pressure. Rigor mortis, algor mortis, and postmortem lividity were present. The hair on the head was 2 cm. in length and light-brown in color; the forehead was prominent, the cheeks puffy and edematous; the eyeballs appeared sunken; the corneas were turbid, the pupils dilated, and the conjunctivas anemic. The fontanels were closed; the tongue was coated. There were three incisor teeth in the upper jaw and two in the lower. The chest appeared normally symmetrical; the costochondral junctions were not enlarged. The abdomen was distended, the liver was palpable, and the testes were in the scrotal sac.

The subcutaneous adipose tissue was marked. The peritoneum was smooth, glistening and of the usual transparency; the intestines were moderately distended; the peritoneal fluid was slightly increased in amount. The appendix appeared normal and lay free in the peritoneal cavity.

The heart lay free in the pericardial sac, which contained about 5 c.c. clear serous fluid. In removing the heart, the fluid blood which escaped con-

tained multiple minute droplets of fat, easily seen in the reflected light. The heart was about the size of the child's fist. The left ventricle was firmly contracted, the right was relaxed; the heart weighed 40 gm. The valves of the heart appeared normal; the myocardium was pale, anemic, and the edge of the freshly cut surface everted.

The lungs lay free in the pleural cavities surrounded by the usual amount of clear serous fluid. The left lung was normal in size, mottled, grayish-red in color; the consistency was normal, and there were present no areas of consolidation. On section, dark, fluid blood escaped from the surface. The lung weighed 50 gm. The right lung was normal in size, weighed 80 gm., floated in water; the consistency was slightly increased, the color mottled grayish-red, and on section dark fluid blood escaped.

The thymus was present in its usual place and measured 2 by 5 cm. It appeared normal.

The liver was enlarged. It extended 3 cm. below the costal arch; the consistence was markedly increased; the superior surface showed indentations of the ribs; the color was bright yellow, that of adipose tissue; it weighed 520 gm. On section, the surface was also bright yellow; it felt fatty; the knife used to cut it was streaked; the parenchyma was swelled, and the cut edge everted.

The spleen was normal in size, the color purplish-red; the consistency was normal; the weight was 15 gm.; on section it appeared normal. There was a small accessory spleen 0.5 cm. in diameter in the gastrocolic ligament.

The left kidney was normal in size and weighed 30 gm.; it was of increased consistency; the color was pale yellowish-red. On section the surface of the cortex was bright yellow, about that of adipose tissue; it felt fatty and streaked the cutting knife; the medulla was bright red. The right kidney presented the same alterations.

The bladder contained 25 c.c. turbid, yellowish urine. The mucosa was pale and anemic. The stomach and intestines appeared normal, and there were present no alterations in the gastric, esophageal or intestinal mucosa.

Microscopic Examination.—In a frozen section of the liver stained with sudan III and hematoxylin there was marked fatty infiltration involving the entire lobule. Regarding the area of the microscopic field as 100 per cent., the morphologic demonstrable fat covers from 70 to 90 per cent of the surface. The only parts free from fat were the blood vessels, the liver capsule, the hepatic canals and the interlobular connective tissue. The liver cells were distended, the nuclei crowded to the sides of the cells; the fat was present as large, discrete globules, 7 to 15 microns, lying within the cells, either single or multiple; the fat globules were highly refractile.

In a section of the kidney similarly prepared, there was present a marked degree of fatty degeneration of the tubules; the glomerules were normal. In a section of the cortex, about three-fourths of the microscopic field was covered by fat, which was present as multiple, fine granules, 1 to 3 microns, of a low refractile index, closely crowded together, occupying the entire cell body of the tubular epithelium. The cells were not increased in size; the nuclei occupied their usual places. The glomerules appeared to have undergone no changes.

In the myocardium there was no evidence of fatty changes. The cytoplasm of the cells appeared granular; the striae were absent; occasional vacuoles were seen. In a section of the lung there were no alterations. Sections of the pancreas, thymus and spleen were normal.

Urine: Twenty-five cubic centimeters of yellowish, turbid urine were obtained from the bladder. It was permitted to remain in a tall glass cylinder in the ice box for several hours, when it separated into a heavy sediment and an opaque supernatant fluid. On microscopic examination of the sediment there were present numerous erythrocytes, epithelial cells, many casts, crystals of ammonium urate and amorphous material. When a drop of sudan III was

added to the sediment, the casts were seen to contain numerous fine, fatty globules of a high refractile index, and within the epithelial cells fine fat granules were also present; free fat was also present in the urine. Examined chemically, sugar, albumin, acetone, and diacetic acid were present.

Blood: Blood removed from the great vessels was similarly placed in a tall glass cylinder. It separated into a supernatant yellowish, milky fluid over a dark red coagulum. On the surface of the fluid there was present a stratum of fat. The fat readily stained with sudan III and was of a high refractile index.

Bacteriology: The following fluids were examined: pleural, pericardial, peritoneal, and heart's blood. In direct smears no organisms were found. Suitable culture mediums were inoculated with each fluid and incubated. No growths were obtained.

Because of the suspicions expressed by one of the parents, a portion of the liver was analyzed chemically for phosphorus, according to the method outlined by Autenrieth.[3] No evidence of phosphorus was found; there was no erosion of any part of the intestine. The bacteriologic examination of the several fluids mentioned was carefully performed, the fluids being removed at the time of the necropsy under strict aseptic precautions, and were inoculated within a few hours into suitable culture mediums and were prepared aerobically and anaerobically; also by the newer bacteriologic methods suggested by Rosenow,[4] including the glucose ascites agar mediums for growing organisms under various degrees of "oxygen tension." All the mediums remained sterile after ten days and were discarded. We concluded that we were not dealing with an infection. We then turned for an interpretation of the disease to the anatomic pathology. Reviewing the necropsy, five significant anatomic alterations were found: lipemia, lipuria, fatty infiltration of the liver, fatty degeneration of the kidneys, anasarca.

Lipemia, or an increase of the fat in the blood, occurs in relatively few pathologic states. It has been found in fat embolism associated with fractures (Scriba[5]); in alcoholism by Gumprecht;[6] in metabolic disturbances by Fischer,[7] who found an increase of over one hundred times the normal fat content in diabetes, and in acidosis by Adler.[8] In fat embolism there is a history of trauma and evidence of the injury; in our patient there was neither. Lipemia in alcoholism, reported by numerous authors, is emphatically denied by Quensel.[9] Further, this cause is ruled out in an infant. Lipemia in a metabolic disturbance has to be considered.

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3. Autenrieth: Detection of Poisons, 1909, p. 4.
4. Rosenow: Jour. Am. Med. Assn., 1914, **63,** 903.
5. Scriba: Deutsch. Ztschr. f. Chir., 1880, **12,** 118.
6. Gumprecht: Deutsch. med. Wchnschr., 1894, **31,** 756.
7. Fischer: Virchows Arch. f. path. Anat., 1903, **170,** 30.
8. Adler: Berl. klin. Wchnschr., 1910, **47,** 1323.
9. Quensel: Alkoholfrågen från Medicinisk Synpunct, Stockholm, 1913, **1,** 144.

Fig. 1.—Colored drawing of the liver, superior surface. The extreme fatty infiltration is evident from the yellowish color, rounded edges and firm consistency.

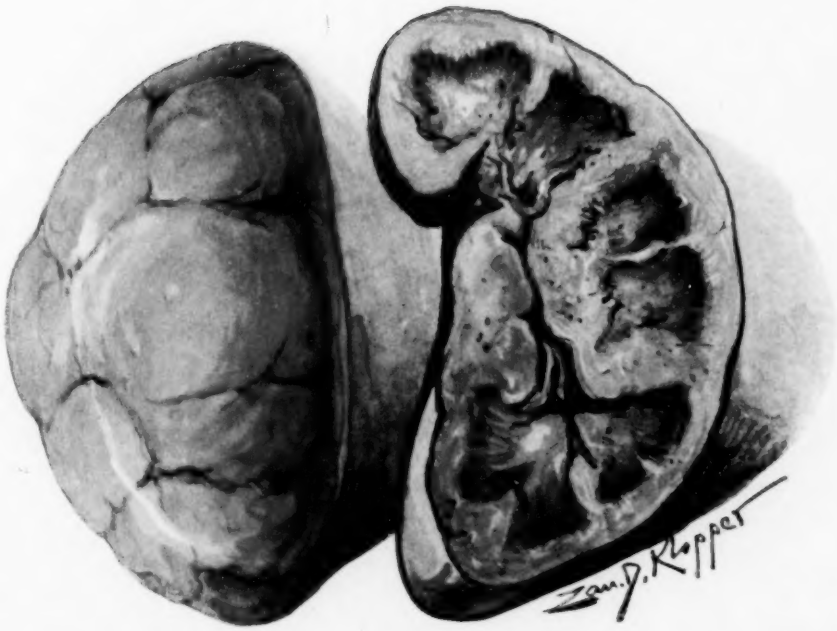

Fig. 2.—Colored drawing of the kidney. Fatty changes are evident from the yellowish, firm outer surface, and the yellowish, swollen cortex of the cut surface and absence of cortical radiations.

Lipuria is usually associated with lipemia, occurring as an outward expression of the increased fat content of the blood, when some of the blood fat is excreted by the kidney into the urine; further, lipemia is apt to occur in those conditions which produce fatty changes in the kidneys, when fat is thrown into the urine as free globules or as fatty casts, from which the fat globules may become loosened as a result of the breaking down of the tubules. In this instance both conditions were present to account for the lipuria; that is, lipemia and fatty kidneys.

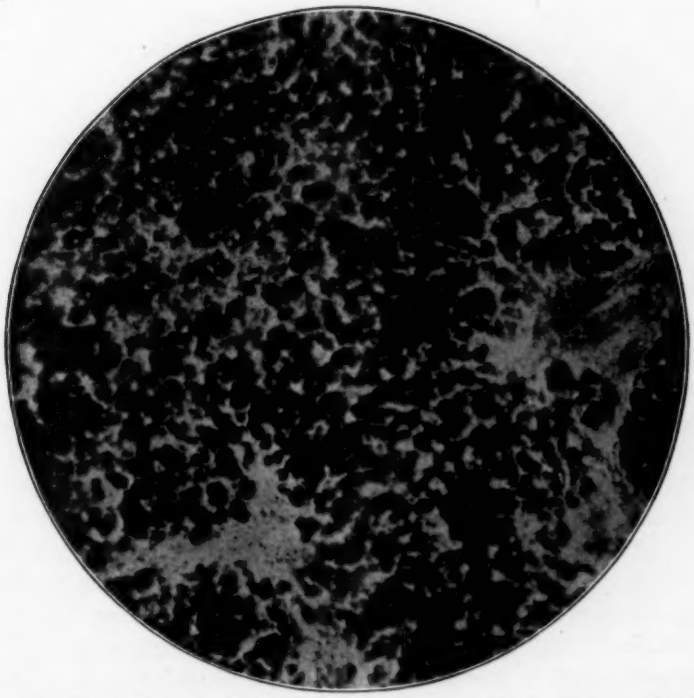

Fig. 3.—Photomicrograph of a frozen section of the liver stained with sudan III and hematoxylin, illustrating the extreme fatty infiltration. All of the dark-staining substance except the blood vessels, connective tissue, and parenchyma cell nuclei, is fat.

In normal liver tissue, employing the ordinary fat stains, little or no fat can be seen microscopically. Fatty infiltration, a condition in which morphologically demonstrable fat occurs, is present in a large variety of conditions. Helly,[10] who studied fatty infiltration in numerous pathologic states, found the fat content of the liver to vary from 7 to 74 per cent., the higher values occurring in conditions associated with metabolic disturbances. Mottram[11] enumerates the diseased states

10. Helly: Verhandl. deutsch. path. Gesellsch., 1914, **17,** 136.
11. Mottram: Canad. Med. Assn. Jour., 1915, **5,** 603.

of the body that are accompanied by fat infiltration of the liver; also those conditions in which the acetone bodies are found increased in the blood and urine. He states that the two series are practically identical. In 1847 Virchow divided the forms of fatty changes of the liver into infiltration and degeneration. These terms have persisted, but they are now regarded as denoting two anatomic types of one alteration. All increased fat of the liver is infiltrated. The liver acts as a fat depot, and the fat in the depot is of the nature and character of the fat given in the food. The fat is present in the liver for physiologic and not pathologic reasons. These general conclusions are asserted by Wells,[12] Mottram[11] and others, and are based on the work of Lebedeff, Rosenfeld and other writers, whom the authors named, cite.

In the normal kidney, also, little or no fat can be demonstrated microscopically, although the fat content (lipins) of the kidney is about 18 per cent. of the dry weight, whereas a pathologic kidney containing but 16 per cent. fat (lipins) of its dry weight may show extreme fatty degeneration. (Wells,[12] p. 365.) An increase in the microscopic demonstrable fat when ordinary fat stains are employed, does not denote an increase in the fat content and is interpreted as fatty degeneration, whereas in the liver an increase is regarded as infiltration. In the kidney of our patient there was a marked fatty degeneration of the tubules, while the glomerules appeared normal. Howell[13] states that the glomerules excrete water and the simple salts, while the tubules excrete substances of a larger chemical molecule, including sugar, urea, albumin, toxins, etc. If the acetone bodies in the blood are excreted into the urine and they are capable of producing fatty degeneration, one would expect to find the fatty changes in the tubules and in the tubules only. Recently Pearce and Brown[14] have produced, experimently, changes in the kidneys of dogs by intravenous injection of arsacetin, in which "the cortex is widened, the striations are yellowish opaque and raised as a result of the tubular necrosis; . . . microscopically, the glomerules are normal, and practically all of the epithelium of the convoluted tubules is necrotic."

The exact mechanism of disease production in acidosis is not clearly understood. Numerous writers have pointed out that it has not been established whether the acidosis is the cause, result, or a concomitant symptom of the disease in which it occurs. In this discussion thus far we have assumed the lipemia as a starting point to explain the pathologic changes. We now hope to point out the relation between the lipemia and acidosis.

Howell teaches that in the normal process of digestion, fat, after its

12. Wells: Chemical Pathology, 1914, p. 361.
13. Howell: Textbook of Physiology, 1910, p. 802.
14. Pearce and Brown: Jour. Exper. Med., 1915, **22**, 517.

emulsification in the intestinal tract, is absorbed by the lacteals of the intestine and is carried by the lymphatics to the thoracic duct which carries it into the blood stream. After each meal there occurs a temporary physiologic increase in the fat content of the blood. Any condition which causes an impairment of the mechanism of removal of the fat from the blood might account for pathologic lipemia. Normally, fat is removed from the blood in three ways: first, it is carried to the fat depots, as the liver, omentum, etc., to be stored; second, it is carried

Fig. 4.—Photomicrograph of a frozen section of the kidney cortex stained with sudan III and hematoxylin. All of the tubules have undergone fatty degeneration, the glomerules are normal.

to the tissues of the body, where it is oxidized to supply body heat; third, it is synthesized to form more complex substances, as lecithin.

In the blood of acidosis there occurs a perceptible increase in acetone, beta-oxybutyric acid and diacetic acid. Marriott[15] has shown that the blood of normal human subjects contains less than 1.5 mg. aceto-acetic acid, and less than 4 mg. beta-oxybutyric acid per 100 gm. blood, the results being expressed in terms of acetone, while in acidosis there is a marked increase. The highest figure he obtained was in

15. Marriott: Jour. Biol. Chem., 1914, **18,** 507.

acidosis of diabetes, in which there was 28 mg. aceto-acetic acid and 45 mg. oxybutyric acid per 100 gm. of blood expressed as acetone.

This excess of acid bodies in the blood is held in neutral state by combination with the alkalies of the blood. In acidosis the "alkali reserve" is thereby diminished. Recent writers have published various observations on the alterations of the hydrogen-ion concentration of the blood in acidosis in which they demonstrate a shifting of the reaction of the blood in the direction of acidity; but at no time can this alteration be marked. Henderson[16] has shown that not more than five parts of excess free H or OH ions can be present in ten billion parts of protoplasm. Wells[17] asserts that acidity is impossible, because death would result from the inability of the blood to carry CO_2, and likewise alkalinity is impossible, because this would cause an increased osmotic pressure which the kidneys would regulate. The acetone bodies in the blood hold in combination molecular proportionate amounts of alkalies which are thereby removed from the function of performing internal respiration; that is, carrying CO_2 to and from the body tissues. With diminished CO_2 carrying power of the blood, the body attempts to compensate by increasing the amplitude and rate of the respiratory movements (Czerny,[18] Henderson[19]); the CO_2 pressure of the alveolar air, nevertheless, falls (Kennaway, Pembrey and Poulton,[20] Howland and Marriott[21]); and because of the lessened oxidation in the lungs, CO_2 is retained in the tissues and internal asphyxia follows. With impairment of oxygenation, the metabolism of fats together with other processes involved in oxidation, become imperfect. This may explain a retardation of the tissues in utilizing the fats of the blood for oxidation and heat production, resulting in fat retention by the blood—lipemia. Further, with imperfect metabolism of the fats, the acetone bodies are formed as intermediate products. It is obvious that a vicious circle soon becomes established, for the greater the amount of acetone bodies in the blood, the more the respiration becomes impaired; and the more respiration is impaired, the greater becomes the production of the acetone bodies; which may explain the rapid course of the disease so frequently observed.

Further, if we follow the principles of Fischer's theory of edema, that the hydration capacity of asphyxiated tissue is tremendously increased, the general edema observed in this instance is explained by the internal asphyxia resulting from the impaired respiration in the lungs and diminished CO_2 carrying power of the blood.

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16. Henderson: Am. Jour. Physiol., 1907, **18,** 250; ibid., 1908, **21,** 427.
17. Wells: Chemical Pathology, 1914, p. 263.
18. Czerny: Jahrb. f. Kinderh., 1897, **45,** 271.
19. Henderson: Jour. Am. Med. Assn., 1914, **63,** 318.
20. Kennaway, Pembrey and Poulton: Jour. physiol., 1913, **48,** 10.
21. Howland and Marriott: Am. Jour. Dis. Child., 1916, **11,** 309.

CONCLUSION

There occurs in acidosis, lipemia from the failure of the body tissues to utilize the fats in the blood.

Lipuria, an outward expression of lipemia, also resulting from the excretion of fat in the waste products of the kidneys as fatty casts.

Fatty infiltration of the liver, which is a physiologic accumulation of fat from the blood.

Fatty degeneration of the kidneys resulting from acid intoxication.

Anasarca resulting from impaired internal and external respiration.

THE OCCURRENCE OF ACIDOSIS WITH SEVERE DIARRHEA *

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INTRODUCTION

The toxic symptoms which may occur in infants suffering from severe diarrhea are striking and characteristic. Prominent features are the evidence of fluid loss (sunken eyes, depressed fontanel and inelastic skin), a mental state which is usually dull and apathetic, often terminating in stupor, but at times characterized by periods of excitement, and increased pulmonary ventilation. The urine of infants thus affected almost regularly contains a reducing substance.[1]

Recently Howland and Marriott[2] have shown that in many cases of this type, especially those showing hyperpnea, there is evidence of acidosis. This evidence was as follows: (1) decreased tension of carbon dioxid in the alveolar air; (2) Sellard's test for the reaction of blood serum; (3) altered hemoglobin dissociation curve; (4) increased tolerance to sodium bicarbonate; (5) increased hydrogen-ion concentration of the blood.

During the past three years we have accumulated data which have a bearing on this subject and which we propose to present at this time. Investigations were made on more than 200 infants. These consisted in the determination of the carbon dioxid in the blood, the carbon dioxid in the alveolar air, the carbon dioxid combining power of blood

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* Submitted for publication Dec. 15, 1916.

* From the New York Nursery and Child's Hospital, The Children's Service at Bellevue Hospital (Dr. L. E. La Fétra, Director), and the Pathological Laboratory of Bellevue Hospital (Dr. Charles Norris, Director).

1. To save space and to avoid needless repetition the presence of these symptoms will be designated by the terms "toxic symptoms" or "intoxication." These terms are not used to designate the complex described by Finkelstein as "Alimentary Intoxication." They are used merely to differentiate the cases of diarrhea without general symptoms from those which show the severe disturbances which frequently occur in the course of this disease.

In twenty cases one of us (O. M. S.) has been able to obtain a sufficient amount of urine to determine with a fair degree of accuracy the nature of the reducing substance. Despite the accepted views of Langstein and Steinitz, von Reuss and others, that this substance is lactose or galactose, our results indicate that dextrose alone, or dextrose in combination with galactose or lactose, is usually present. The details will be the subject of a later communication.

2. Howland, J., and Marriott, W. McK.: Acidosis Occurring with Diarrhea, AM. JOUR. DIS. CHILD., 1916, **11**, 309.

plasma, the tolerance to sodium bicarbonate, the presence of acetone bodies in the urine and the ammonia coefficient of the urine.

I. THE CARBON DIOXID OF THE BLOOD OR ALVEOLAR AIR AND THE CARBON DIOXID COMBINING POWER OF BLOOD PLASMA

1. *The Carbon Dioxid Content of the Blood.*—The determinations were made by the method of Barcroft and Haldane.[3] Blood was collected over mercury in modified Brodie pipets and herudin was used to prevent coagulation. In most instances the determinations were made in duplicate, and always when the values were low.

In twenty infants not acutely ill and free from digestive disorders the values ranged from 36 to 46 volumes per cent.[4] In infants affected with severe diarrhea accompanied by toxic symptoms, the carbon dioxid was much reduced (Table 1).

TABLE 1.—CARBON DIOXID IN BLOOD IN SEVERE DIARRHEA WITH TOXIC SYMPTOMS

Case	CO_2, Volume per Cent.	Case	CO_2, Volume per Cent.	Case	CO_2, Volume per Cent.
1	26	10	16	19	26
					22
2	18	11	24		
			20	20	30
3	19				27
		12	19		
4	21			21	29
	23	13	25		19
5	19	14	23	22	26
	18		21		
				23	23
6	17	15	24		
	21			24	28
		16	21		23
7	19		17		
				25	24
8	22	17	24		
			21	26	27
9	27				
	19	18	19		

2. *The Carbon Dioxid Combining Power of Blood Plasma (Van Slyke).*—The estimations were made according to the technic of Van Slyke.[5] Blood was collected, with sufficient potassium oxalate to make a concentration of about 1 per cent., centrifugalized immediately, and when the determination could not be made at once, the plasma was kept on ice in paraffined bottles until used. In most instances the

3. Barcroft, J., and Haldane, J. L.: A Method for Determining Oxygen and Carbon Dioxid in Small Amounts of Blood, Jour. Physiol., 1902, **28,** 232.

4. These figures represent venous blood and are accordingly higher than those which would hold for arterial blood or alveolar air.

5. Van Slyke, D. R.: Proc. Soc. Exper. Biol. and Med., 1915, **12,** 165.

determinations were made within twenty-four hours. The cases may be separated into four groups.

a. Infants not Acutely Ill and with no Digestive Disorder.—The values ranged from 46.2 to 76.1 volumes per cent. of carbon dioxid (Table 2). The fact that infants may show lower values than adults has been noted by Van Slyke. Our determinations did not show uniformly low values, but rather a wide variation, with a tendency to be lower than in adults. In a number of cases the figures were the same as for normal adults.

TABLE 2.—Carbon Dioxid Combining Power of Blood Plasma (Van Slyke) in Normal Infants *

Number	Age	Weight, Pounds	CO_2, Volume per Cent.	Number	Age	Weight, Pounds	CO_2, Volume per Cent.
1	3 weeks	7	58.6	15	6 months	13¾	47.1
2	4 weeks	6½	49.0	16	7 months	13	53.8
3	4 weeks	8	54.8	17	8 months	15½	56.7
4	5 weeks	8½	46.2	18	8 months	14¾	50.0
5	6 weeks	9	52.8	19	8 months	15	51.0
6	6 weeks	8¾	75.8	20	9 months	13½	46.2
7	8 weeks	10	59.5	21	11 months	14½	54.8
8	9 weeks	10½	55.7	22	12 months	19½	51.9
9	3 months	10	54.8	23	13 months	21¾	60.5
10	3½ months	10½	56.7	24	13 months	19	61.4
11	3½ months	9¾	48.1	25	16 months	18¾	51.0
12	4 months	12	55.7	26	17 months	24	61.4
13	4 months	11½	53.8	27	18 months	22	63.3
14	6 months	14	49.0				

* These infants were normal in the sense that they were suffering from no acute illness or digestive disorder. They all, however, were under weight.

Although we attempted to take the blood for examination about one-half hour before feeding (from two and a half to three and a half hours after feeding), this time often varied, and it seemed of interest to determine whether digestion had an influence in causing the low results. Accordingly, we made determinations directly before and directly after feeding in six infants, and in another series, directly before and one hour after feeding (Table 3). These observations, while they show a rise in carbon dioxid after feeding,[6] give no explan-

6. That such a rise occurs is well known and has been demonstrated by the following observers: Porges, Leimdorfer, and Markovici: Ztschr. f. klin. Med., 1911, **73,** 389; Hasselbach: Biochem. Ztschr., 1912, **46,** 403; Higgins: Am. Jour. Physiol., 1914, **34,** 114.

ation for the low values at times found in normal infants. We also tabulated the cases on the basis of the variety of food and method of feeding but found no constant relationship between either and the carbon dioxid values.

In the absence of a definite explanation we can only state that in apparently normal infants the carbon dioxid combining power of blood plasma varies within rather wide limits. It seems possible, as Marriott suggests, that the low carbon dioxid values at times obtained in infants result from their more active metabolism, leading to a disproportionately greater production of acids.

b. Cases of Minor Nutritional Disorders.—In this group were twenty infants who were not acutely ill, but who were gaining slowly or not at all, and presented mild digestive symptoms such as occasional vomiting and stools which were of abnormal character or frequency. The carbon dioxid ranged from 48.1 to 67.2 volumes per cent. and was therefore within the limits of normal.

TABLE 3.—The Influence of the Ingestion of Food on the Carbon Dioxid Combining Power of Blood Plasma

Number	CO_2, Volume per Cent.		Number	CO_2, Volume per Cent.	
	Directly Before Feeding	Directly After Feeding		Directly Before Feeding	One Hour After Feeding
1	52.8	56.8	1	47.1	49.0
2	60.5	67.6	2	53.8	54.9
3	62.4	64.3	3	53.8	54.8
4	50.0	52.8	4	59.5	60.5
5	55.7	57.6	5	62.0	69.5
6	54.8	56.8	6	62.0	63.8

c. Cases of Diarrhea.—These infants were suffering from moderate or severe diarrhea, but at the time the examination was made did not present definite toxic symptoms. This group is of special interest, as most cases of intoxication are preceded by diarrhea[7] (Table 4). In a number of instances the carbon dioxid was decreased in the absence of severe general symptoms, and served as a warning of developing intoxication. It is of interest also that there was no pronounced increase in the frequency or depth of the respirations. Of further interest is the fact that in three cases (5, 9, 17) the diarrhea terminated fatally, and there was no reduction in the carbon dioxid.

7. Although this is usually true, yet cases occur which present the typical symptoms of intoxication without diarrhea. There were four cases in this series with the toxic symptoms often associated with diarrhea, but with no history of diarrhea and none during observation.

d. Cases of Intoxication.—There were twenty cases of intoxication, and in eighteen the carbon dioxid combining power of the blood plasma was greatly reduced (Table 5). In Cases 6 and 13 hyperpnea was not observed, but with this exception the symptoms were distinct. In both

TABLE 4.—CARBON DIOXID COMBINING POWER OF BLOOD PLASMA IN INFANTS WITH DIARRHEA BUT SHOWING NO TOXIC SYMPTONS

Number	Age, Months	CO_2, Volume per Cent.	Remarks
1	4	38.5	Developed intoxication*
2	4	58.4	Recovered
3	5	57.6	Recovered
4	5	32.8	Developed intoxication*
5	5	55.7 - 58.6 - 56.7	Died; no symptoms of intoxication
6	6	42.4	Developed intoxication*
7	6	51.0	Recovered
8	6	46.2	Recovered
9	6	48.1 - 51.0 - 50.0	Died; did not develop intoxication
10	7	45.3	
11	7	59.5	Died†
12	7	60.5	Recovered
13	8	31.9	Developed intoxication*
14	8	30.0	Developed intoxication*
15	9	55.7	Recovered
16	9	54.8	Recovered
17	9	55.7	Died†
18	10	32.8	Developed intoxication*
19	10	30.0	Developed intoxication*
20	11	53.8	Recovered
21	11	57.6	Died†
22	11	51.9	Recovered
23	12	52.8	Recovered
24	12	42.4	Developed intoxication*
25	13	49.0	Recovered
26	13	51.0	Recovered
27	13	54.8	Recovered
28	14	55.7	Recovered

* The symptoms of intoxication developed within two days after this determination was made.

† In Cases 11, 17 and 21 no further carbon dioxid determinations were made. In all three cases, however, death occurred within forty-eight hours and the infants were very ill at the time of observation.

cases there was no decrease in the carbon dioxid combining power of the blood plasma. The estimations were made in duplicate and on two separate occasions.

3. *Carbon Dioxid Content of Alveolar Air.*—By a method of air collection similar to that used by Howland and Marriott[8] the alveolar air was analyzed in the Haldane apparatus. Such analyses were made on expired air from normal infants, infants suffering from simple diarrhea and infants with intoxication. The results were practically identical with those obtained by Howland and Marriott and those obtained by us with other methods. It is therefore unnecessary to cite these results in detail, but some of them will be referred to later.

TABLE 5.—CARBON DIOXID COMBINING POWER OF BLOOD PLASMA IN INFANTS WITH INTOXICATION *

Number	Age, Months	CO_2, Volume per Cent.	Number	Age, Months	CO_2, Volume per Cent.
1	2	20.4	11	7	18.5
2	3	17.6	12	7	24.2
3	3	21.4	13	8	56.7 54.8
4	4	26.2	14	8	27.1
5	4	23.3	15	8	30.9
6	5	51.9 52.8	16	9	25.2
7	6	12.8	17	9	18.5
8	7	26.2	18	11	25.2
9	7	27.1	19	11	37.6
10	7	19.5			

* In a number of these cases several determinations were made, but only the lowest values are given in the table.

DISCUSSION OF RESULTS OF CARBON DIOXID DETERMINATIONS

It is unnecessary to consider in detail the significance of the carbon dioxid content of the blood or expired air, as this subject and the literature have been discussed by Peabody,[9] Higgins and Means,[10] Howland and Marriott,[11] Marriott[12] and others. It seems definitely established that with the exception of unusual conditions such as diminished excitability of the respiratory center or altered permeability of the respiratory epithelium, a reduction of the carbon dioxid of the blood signifies a diminution of the fixed alkali of the blood and therefore a condition of acidosis.

8. This method is an adaptation to infants of the Plesch-Higgins method. Plesch: Ztschr. f. exper. Path. u. Therap., 1909, **6,** 380; Higgins: Pub. 203, Carnegie Inst., Washington, D. C., 1915, p. 168.

9. Peabody, F. W.: Some Aspects of the Clinical Study of the Respiration: The Significance of Alveolar Air Analysis, Am. Jour. Med. Sc., 1916, **151,** 184.

10. Higgins and Means: Jour. Pharmacol. and Exper. Therap., 1915, **7,** 1.

11. Howland and Marriott: Bull. Johns Hopkins Hosp., 1916, **27,** 63.

12. Marriott: Arch. Int. Med., 1916, **17,** 840.

Our results, therefore, agree with those of Howland and Marriott, that in the intoxication due to diarrhea there is usually a distinct acidosis.

The only clinical sign which is at all characteristic is the increased pulmonary ventilation or hyperpnea. This sign when unaccompanied by cyanosis is almost diagnostic. From physiologic considerations one would expect an increase in the respirations whenever there was a pronounced lowering of the carbon dioxid. This, however, was not true in all of our cases. In 65 patients with a pronounced reduction of the carbon dioxid of the blood or alveolar air, the presence or absence of hyperpnea was noted in 40. It was present to some degree in 31 and absent in 9. These patients, however, were examined only once or twice a day and it seems quite possible that the increased pulmonary ventilation may be intermittent and might thus be overlooked. That these patients were actually suffering from acidosis is borne out by the fact that in 5 the carbon dioxid became normal after the administration of sodium bicarbonate.

II. TOLERANCE TO SODIUM BICARBONATE

It has been shown by Sellards[13] and by Palmer and Henderson[14] that the amount of sodium bicarbonate required to render the urine alkaline is fairly constant in normal adults, and that in acidosis the tolerance is much increased.

Our first consideration was the tolerance of infants not affected with acidosis.[15] The administration of the sodium bicarbonate was controlled by a preliminary carbon dioxid determination to exclude the presence of acidosis, and a test of the reaction of the urine to litmus to be sure that it was acid before the bicarbonate was administered.

Infants from 3 to 12 months old required from 1.25 to 3.25 gm. of sodium bicarbonate when given in a single dose by mouth to render the urine alkaline (Table 6). There is no regular and definite correspondence between the amount of sodium bicarbonate required and the age or weight, but as a rule the older, heavier infants required larger amounts; but these amounts were in no way directly proportional to age or weight.

When we came to determine the tolerance of infants with acidosis we found that the administration of large doses of sodium bicarbonate

13. Sellards: Bull. Johns Hopkins Hosp., 1914, **25,** 141.

14. Palmer and Henderson: Arch. Int. Med., 1913, **12,** 153.

15. Our conception of the tolerance of normal infants to sodium bicarbonate is the single dose necessary to render the urine alkaline. In cases of acidosis the point of tolerance is indicated by the single dose of sodium bicarbonate necessary to raise the carbon dioxid to normal. In making the determinations we gave gradually increasing amounts (0.2 to 0.6 gm. increase at each dose) of the drug at intervals of five to eight hours until the proper dose was reached.

by mouth was an unsatisfactory procedure. Even normal infants frequently vomit, and this was so often true of those with severe diarrhea that the method was abandoned. We were able to determine the tolerance in six cases, and found that it was much increased (Table 7).

The subcutaneous method was not used, as the sodium bicarbonate is partly changed to carbonate by heating, and sodium carbonate is very

TABLE 6.—Amount of Sodium Bicarbonate by Mouth Necessary to Render the Urine Alkaline. Normal Infants

Number	Age, Months	Weight, Pounds	Sodium Bicarbonate, Gm.	Number	Age, Months	Weight, Pounds	Sodium Bicarbonate, Gm.
1	3	11	1.75	10	8	16½	2.75
2	4	12	2.0	11	9	16¾	2.75
3	4	11¾	2.25	12	9	17	3.0
4	5	13	2.25	13	10	18	2.50
5	5	13½	2.75	14	11	17½	2.75
6	6	14½	2.25	15	12	20	3.0
7	6	15	2.5	16	12	20	3.0
8	7	15½	2.5	17	12	19½	3.75
9	8	16	2.25	18	12	19	3.25

TABLE 7.—Amount of Sodium Bicarbonate by Mouth Necessary to Render the Urine Alkaline and to Cause Increase of Carbon Dioxid of Blood or Alveolar Air to Normal. Intoxication

Number	Age, Months	Weight, Pounds	CO_2 Before Giving Alkali	CO_2 After Giving Alkali	Sodium Bicarbonate, Gm.
1	4	9	21	48	6.0
2	5	9½	19.6	40	7.0
3	6	10¾	24	49	5.5
4	6	12½	26	52	6.5
5	6	13	23	45	7.0
6	7	14	19	51	6.5

irritating when given subcutaneously. It is possible to change any sodium carbonate thus formed by passing carbon dioxid through the solution (Magnus-Levy), but owing to the ease and safety of intravenous injections the latter method was used.

Doses of 1 to 2 gm. of sodium bicarbonate intravenously are sufficient to render alkaline the urine of infants not affected with acidosis. This is not only smaller than the amount required by mouth, but it was

noted also that when administered per os it was often one to three hours before the urine became alkaline, while by the intravenous method it required usually only one-half to one and a half hours. The tolerance of fifteen infants with acidosis showed the same results. The effect was more prompt and the dose required was smaller (Table 8).

Our results show, therefore, that in intoxication there is a great increase in the tolerance to sodium bicarbonate. They demonstrate also that the intravenous method gives a prompter result and with a smaller dose.

TABLE 8.—THE AMOUNT OF SODIUM BICARBONATE BY INTRAVENOUS INJECTION NECESSARY TO RENDER THE URINE ALKALINE AND TO INCREASE THE CARBON DIOXID OF BLOOD OR ALVEOLAR AIR TO NORMAL. INTOXICATION

Number	Age, Months	Weight, Pounds	CO_2 Before Giving Alkali	CO_2 After Giving Alkali	Sodium Bicarbonate, Gm.
1	4	8	25	39	3.5
2	4	8½	21	47	3.0
3	5	9	19	50	3.5
4	5	11	23	43	4.0
5	5	10½	20	54	5.0
6	7	12	22	45	3.5
7	7	13	21	41	4.0
8	7	12	17	47	5.0
9	8	14	19	46	5.5
10	8	11	24	50	5.0
11	8	13	20	48	4.5
12	10	14	18	39	5.5
13	11	13½	26	46	5.5
14	12	14½	22	44	6.0
15	12	16½	20	49	5.5

III. THE AMMONIA COEFFICIENT IN THE URINE

The quantity of ammonia excreted in the urine and its ratio to the total nitrogen varies greatly in small infants and bears relationship to the type of food. Very high values are sometimes obtained in infants with malnutrition or diarrhea in the absence of any noticeable change in the carbon dioxid of the blood or alveolar air. The presence of a high ammonia coefficient cannot therefore be accepted as conclusive evidence of acidosis, at any rate not in the present conception of the term.

We made determinations of the ammonia in 16 cases of intoxica-

tion. In 14, the coefficient was above 20. In two instances it was 8 and 12.5, respectively, which are not unusual figures for infants with nutritional disorders.

IV. PRESENCE OF ACETONE AND DIACETIC ACID IN THE URINE

The urine of many infants with intoxication showed a small or moderate amount of acetone and diacetic acid. These substances were not present in amounts proportional to the severity of the symptoms or to the degree that the carbon dioxid was reduced. Indeed, in three of the severest cases of acidosis (carbon dioxid tension of alveolar air 16, 18 and 19, respectively) acetone bodies could not be demonstrated in the urine. Since most of the infants with intoxication were on diets which represented at least partial starvation, the presence of small amounts of acetone bodies in the urine is without significance. Howland and Marriott found no significant increase in the acetone bodies in the blood or urine of their patients.

GENERAL DISCUSSION

The onset of intoxication is usually gradual and follows, in most cases, a sharp attack of diarrhea. In a number of instances we have made determinations of the carbon dioxid in infants suffering with nutritional disorders, and by this means were able to determine the onset of acidosis. The following case serves as an illustration:

Baby F., aged 6 months, weight 13 pounds. For about a week there had been a slight loss of weight and the patient had from three to six slightly loose stools each day. June 10 the carbon dioxid of the venous blood was 40 volumes per cent. The infant became worse, and successive daily determinations showed carbon dioxid of 37, 30, 28, 24, and 15 volumes per cent., respectively. It was only when the carbon dioxid reached 24 that the respirations became noticeably exaggerated and the toxic symptoms became marked.

In some instances the onset of the acidosis is sudden and the carbon dioxid value of one day may be normal and that of the next day show a decided reduction.

Not all cases of severe diarrhea terminate in acidosis, and as Howland and Marriott point out, the disease may end fatally and be accompanied at no time by reduction of the carbon dioxid values. We have seen several well marked cases of intoxication which presented the usual symptoms, with the exception of hyperpnea, and in which there was at no time any reduction in the carbon dioxid and no increase in the tolerance to sodium bicarbonate or improvement after its administration. The following case was of this type:

Baby D., 7 months old, had diarrhea for one week. There were four to fifteen green watery stools a day and occasional vomiting. The fontanel was sunken, there was evidence of great loss of weight, the skin was dry and inelastic. The mental condition was dull, although at times the baby was excited and would emit loud, sharp cries. The respirations were not noticeably increased in rate or depth.

Time	Carbon Dioxid, Venous Blood, Volumes Per Cent.	Carbon Dioxid Tension, Alveolar Air, Mm.	Urine
10 a. m.	41.0	39.0	Acid
11 a. m.	42.2	41.3	

Three grams of sodium bicarbonate were given by intravenous injection.

Time	Carbon Dioxid, Venous Blood, Volumes Per Cent.	Carbon Dioxid Tension, Alveolar Air, Mm.	Urine
12 m.	44.4	42.2	Alkaline
1 p. m.	44.6	43.0	Alkaline

There was no improvement in the symptoms and death occurred at 6 p. m.

Such cases demonstrate that intoxication is not always accompanied by acidosis, and in the absence of hyperpnea the diagnosis must rest on laboratory evidence.

Treatment.—The acidosis is best treated by the administration of sufficient sodium bicarbonate to increase the carbon dioxid to normal or to render the urine alkaline. Provided that the urine is tested fresh, the two tests are of about equal value and in a number of cases we found that almost coincidently the urine became alkaline and the carbon dioxid normal.

According to our experience, the most satisfactory method of administration is by intravenous injection. It is a very difficult matter for these infants to take by mouth and to retain the required amount of alkali, and unless a sufficient quantity be given the treatment is practically useless. We have also tried the administration of sodium bicarbonate by rectal instillation (Murphy drip), but the results were unsatisfactory. The fluid was usually expelled, and in no instance was a sufficient amount absorbed to influence the carbon dioxid values. To give the alkali subcutaneously requires careful preparation of the solution and the injection of a comparatively large amount of fluid in relation to the size of the infant.

The intravenous injection of 75 to 150 c.c. of a 4 to 5 per cent. solution of sodium bicarbonate is usually sufficient for the first treatment.[16] If the dose is adequate the carbon dioxid becomes normal and

16. If a scalp vein of sufficient size is evident this may be used. In most instances, however, it is necessary to expose a vein by incision or to give the injection into the superior longitudinal sinus. (Tobler: Monatsch. f. Kinderh., 1915, **13,** 384; Helmholz: Am. Jour. Dis. Child., 1915, **10,** 194.) The latter seems preferable in every way. The fluid is best given by gravity and should be given slowly. A cylinder with a capacity of 30 to 100 c.c. may be used. One end of a piece of rubber tubing is attached to the cylinder and the other end has a connecting tip which fits into the needle. It is of advantage to have a stopcock either at the end of the cylinder or near the end of the tubing. The needle is inserted with a small syringe attached, and by slight aspiration one can determine whether the sinus has been entered. If so, the syringe is detached and the apparatus for the injection, which has been filled and the air expelled, is connected. A needle ½ inch long, of 20 to 22 gage, and with a short, bevel point, is of advantage in entering the sinus.

in many instances above normal, hyperpnea ceases and there is great improvement in the general appearance of the patient. This change is very striking to observe: the face loses its drawn appearance, the patient becomes alert and comfortable and the skin softer and more elastic.

Whether the first dose of bicarbonate is sufficient can be determined by the change in the carbon dioxid[17] and the general improvement in the patient. In addition to the intravenous injection it seems advisable to give sodium bicarbonate by mouth in 2 to 5 per cent. solution so that the patient will receive 2 to 5 gm. per diem in this manner. Within eight hours a second intravenous injection should be given if necessary. The necessity for repeated injections has been present in most of our cases, and the best results have been attained in those which were most carefully observed and the sodium bicarbonate repeated as soon as the carbon dioxid is again below normal.

Unless the infant is moribund, improvement frequently occurs, but despite this improvement the patient often succumbs. Death has occurred in 86 per cent. of the cases with which this paper is concerned. These results, however, include the earlier cases, in which the infants were not thoroughly treated, and also a number of infants who survived the acidosis, but died later of malnutrition. The results in our more recent cases have been more satisfactory.[18] In the cases in which the acidosis has been thoroughly treated, the fatal outcome has been due to one of two causes. 1. Recurrence of the acidosis. This has occurred in a few instances and the acidosis has been very acute and quickly fatal. 2. The usual circumstance is that the infant develops malnutrition of a very severe grade and despite all resources of feeding, gradually wastes away. It would seem that there is some profound disorder of metabolism of which the acidosis merely is a symptom.

There remains one point for further discussion, namely, the dietetic treatment. At present little that is definite and positive can be said, and a successful dietetic therapy can be achieved only by a thorough understanding of the basic nutritional fault. We have usually given nothing save the bicarbonate solution, or water, for the first twenty-four to seventy-two hours. Later we have given some form of cereal gruel and then diluted protein milk. The sugar has been kept low for some days and carbohydrate given mainly in the form of cereals.

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17. For several months we have used the colorimetric apparatus devised by Marriott (Jour. Am. Med. Assn., 1916, **66,** 1594) which greatly simplifies the determination of carbon dioxid in alveolar air. A comparison with other methods has shown that the results are sufficiently accurate for all clinical purposes.

18. This series of cases is still incomplete and will be the subject of a further report.

Owing to the frequent presence of sugar in the urine and a normal or increased blood sugar in these cases, we deem this procedure advisable.

SUMMARY

Infants suffering from severe diarrhea with toxic symptoms often show the following signs of acidosis: 1, decrease of the carbon dioxid of the blood and alveolar air; 2, decreased carbon dioxid combining power of the blood plasma; 3, high ammonia coefficient in the urine; 4, increased tolerance to sodium bicarbonate; 5 improvement of the symptoms after administration of sodium bicarbonate.

These signs are evident in some cases of diarrhea before the typical symptoms of intoxication have developed, and serve as a warning and therapeutic indication.

If an infant suffering from severe diarrhea has hyperpnea, the diagnosis of acidosis is almost certain. If hyperpnea is not observed the diagnosis of acidosis must rest on laboratory evidence.

Thorough and carefully controlled treatment by sodium bicarbonate usually causes disappearance of the acidosis, but despite this, the infants frequently die from a severe form of malnutrition.

We desire to thank Dr. L. E. La Fétra for the use of the material from his wards at Bellevue Hospital, and Drs. R. G. Freeman, C. G. Kerley and C. F. Collins for the cases from the Nursery and Child's Hospital. The determinations of the carbon dioxid combining power of blood plasma were made in the laboratory of Dr. A. O. Gettler at Bellevue Hospital, to whom we are indebted for this privilege and for much assistance.

FAMILIAL ICTERUS OF NEW-BORN INFANTS

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Pfannenstiel[1] gave the first detailed description of familial icterus of new-born children. He described two fatal cases and collected the scattered reports in the literature. The cause of familial icterus of new-born children is unknown. The disease has nothing in common with Buhl's or Winckel's disease. There is no evidence to prove that familial icterus is due to septic processes. It is not present at birth, but appears during the first days of life. In none of the cases is there a history of birth injury, nor does it seem to be due to toxemia of pregnancy. Most of these children are strong, robust and mature at birth. One might say that the children are in a sense physically defective and very soon become incapacitated to carry on extra-uterine existence. It is possible that the liver failed in the performance of its extra-uterine function.

The disease may occur in successive pregnancies. Occasionally normal children are born, and later children die a few days after birth as the result of a grave and progressive icterus. As a rule, there is no hereditary influence, nothing of a similar nature is discovered in the family of the father or mother. The disease begins usually on the first or second day of life and rapidly increases in severity. Pfannenstiel briefly described the symptoms by referring to the presence of catarrhal conditions of the mucous membrane, sometimes with bloody discharge, though true melena does not occur. The stools are catarrhal in character and are frequent; the urine contains bile pigment; the patient may show meningeal irritation, with characteristic crying and whining. At the onset there may be hyperemia of the skin. If the disease continues, hemorrhages from the various mucous surfaces and into the skin, as well as from the umbilicus, occur; death follows soon from collapse. Atonic convulsions, particularly of the upper extremities, as well as opisthotonos, are frequently observed. Pfannenstiel called attention to the fact that the disease bears no relation to syphilis, and in one case in which a necropsy was made and the liver and the spleen were examined histologically, no evidence of syphilis was discovered, and no spirochetes were found.

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* Read before the Twenty-Eighth Annual Meeting of the American Pediatric Society, held at Washington, D. C., May 8-10, 1916.

1. Pfannenstiel, J.: Ueber den habituelle Ikterus gravis der Neugeborenen, München. med. Wchnschr., 1908, **55**, 2169, 2233.

Knopfelmacher,[2] who reviews the literature in a critical way, is inclined to think that after all some septic process might be invoked to explain this group of cases. For example, in one of Pfannenstiel's reported cases pericarditis, hemorrhages into the serous cavities and swelling of the kidneys led him to think that possibly an infection had taken place. He even thinks that the habitual occurrence of the disease in the same family is not sufficient argument against the consideration of sepsis. He considers that a chronic infection of the vaginal portion of the birth canal of the mother may serve as the origin of infection in the successive cases.

I should be inclined to believe from my own observation that the septic nature of this disease has not been proved.

The familial form of the disease is not a frequent one if we may judge from the reports of clinicians. Thus, H. Rehn[3] of Frankfort, in connection with a clinical report on one case, remarks that it is rare, and he states that in his fifty years' practice he had not met any similar cases until this one.

The disease under consideration, that is, familial icterus of the new-born, has nothing in common with chronic family jaundice, which is characterized by the fact that it may be present at birth, and it may persist throughout life, or that it may first occur during adolescence. In chronic jaundice the patient experiences but little inconvenience and may attain an advanced age. The enlargement of the spleen in chronic jaundice is a constant feature. Familial icterus of the new-born must also be differentiated from congenital obliteration of the bile duct. This obliterating disease is characterized by intense obstructive jaundice.

Isolated cases of habitual familial jaundice are described in the literature. McGibbon[4] records a family of six children, the oldest of whom was normal, the other five having jaundice. The fourth child was prematurely born; the other four children died of severe icterus between the third and seventh day of life.

Cornelius May[5] described a family in which the father and mother were perfectly normal, with no infections and no syphilis. The first child, born at full term and apparently normal, developed icterus in twelve hours and died on the third day. The second child, fairly well

2. Knopfelmacher: Der habituelle Icterus neonatorum gravis, Ergebn. d. inn. Med. u. Kinderh., 1910, **5,** 205.

3. Rehn, H.: Zur Kasuistik des habituellen familiären Ikterus der Neugeborenen, Jahrb. f. Kinderh., 1912, **75,** 358.

4. McGibbon, John: Fatal Cases of Jaundice in the New-Born Child, with Notes of a Case in Successive Pregnancies, Edinburgh Obst. Soc., 1912-1913, **38,** 285.

5. May: Beitrag zur Kenntnis des Ikterus Neonatorum gravis, Arch. f. Kinderh., 1911, **56,** 313.

developed, born one year later, apparently normal, became icteric in six hours and died in two days. The third child, born three years later, apparently normal, developed intense icterus in twenty-four hours. The mother began to secrete breast milk on the third day, though the baby seemed too weak to nurse. The neck became rigid, the child cried and whined, convulsions occurred, and with increasing coma death followed on the twelfth day after birth. The necropsy showed no tissue changes or bacteriologic findings. The fourth child, born after three years, gives a very similar history. It developed icterus on the second day. The child was given breast milk, but gradually lost in weight, became comatose and died on the sixth day.

Postmortem examinations have shown a peculiar icteric discoloration of the larger nuclei in the basilar portion of the brain and also a yellowish discoloration of the nuclei in the medulla. This has been described as nuclear icterus. In some instances the cells in the anterior gray portion of the spinal cord are stained yellow. Orth observed the same condition in the brain cells of children who suffered from the milder form of icterus neonatorum.

Pfannenstiel considers that the most important anatomic changes which exist in the so-called nuclear icterus (Kern icterus) are swelling of the spleen, hypertrophy of the liver without microscopic alterations in the structure of the organ, and a tendency to transudations into the serous cavities and into the ventricles of the brain. Catarrhal conditions of the mucous membranes in the digestive tract and minute hemorrhages on the serous and mucous surfaces are recorded, though fatty and other degenerative processes of glands and organs are absent.

I have encountered examples of familial icterus of the new-born in two families. The first case occurred in an Italian family. The baby in question was referred to me through the kindness of Dr. DeLee of the Chicago Lying-In Hospital and Dispensary. The history is as follows:

The mother and the father were 28 years of age. They were both born near Naples, the mother having lived in this country ten years and the father fifteen years, and they had been married nine years. The mother had pneumonia five years before and was very ill at that time. She had never had any surgical operation, and with the exception of the illness mentioned above, she had always been well. She had four brothers and one sister living and well and in none of their families had a similar diseased condition occurred. The mother's mother died the year before of pneumonia. The mother herself had been well during all of the previous pregnancies. The father's mother was living and well; his father died in Italy from some unknown cause. The father, a barber by occupation, said he had never been sick. The mother had borne five children, of whom two were living and three dead. In addition to this there had been two miscarriages, each occurring at three months. These constituted the second and fourth pregnancies. The first and the second babies were born well and remained so up to that time. The third baby seemed strong and robust at birth, but developed jaundice on the second day and on the

third day the jaundice had deepened greatly, the baby being more or less comatose, having frequent convulsive attacks and dying on the third day. The fourth baby sickened on the second day, jaundice becoming intense, convulsions ensuing and death occurring on the third day, as in the previous case.

The family came under my observation with the birth of the fifth child. The history of the last baby does not differ materially from those already described. The child sickened on the first day, icterus became very marked, the child vomited occasionally, bowel movements became somewhat frequent, there was no elevation of temperature, convulsions occurred on the second day, and the child became comatose and died on the fourth day.

The second case occurred in a Russian Jewish family. The father had always been well and denied venereal infection. The mother had had the usual diseases of childhood. Six years before, on account of abdominal pain and symptoms referable to the gallbladder, an operation was performed and the gallbladder was removed. Two or three months after this operation her tonsils were removed. The mother was about 32 years of age and the father was three years her senior. She had borne six children. When her first baby was born the mother was about 21 years of age. This child, a boy, is living and is 11 years old. He had scarlet fever when 6 years of age. His urinary examination shows albumin and casts, and he has a chronic nephritis. The second child is living and well. The third pregnancy resulted in a miscarriage. The fourth child was born robust, but became jaundiced on the second day, was seized with convulsions, had frequent stools, the jaundice became more and more intense, and he died on the third day. I was enabled to examine the fifth child. The mother was delivered at Michael Reese Hospital in May, 1914, in the service of Dr. Lester E. Frankenthal. The child was born apparently well and strong. On the first day he developed jaundice, which rapidly became intense; hemorrhages occurred from the nose and throat and under the skin, and convulsions took place at intervals; vomiting and diarrheal stools were observed, and the baby died on the third day. A necropsy was performed, which showed some enlargement of the liver and spleen, though no other pathologic changes of any moment could be noted and bacteriologic examinations showed the tissues to be sterile. The bile passages were of normal size and showed no obstruction.

The sixth baby was born April 22, 1915, in the service of the Chicago Lying-In Hospital and Dispensary. Delivery was rapid and easy, and there was no asphyxia at birth, the child crying vigorously. The baby became icteric on the second day. The umbilical wound was normal. The child voided bile-stained urine, but had the normal number of stools. The temperature was about 99. The child resented palpation of the abdomen, and it was thought that there was some tenderness over the liver. The baby cried much and the jaundice deepened materially. The child slept most of the time, nursed very poorly, did not take water, and whined weakly. The conjunctivae became icteric and the yellowness of the skin increased markedly. The urine decreased in quantity, the temperature remained at 99, and the baby seemed very somnolent and toxic. There were no petechial spots and no hemorrhages. On the fourth day the temperature was still 99 and the icterus was more marked. The baby refused food, except as it was forced. The liver was enlarged, but the spleen was not palpable. The somnolence increased and the condition seemed grave. On the fifth day the baby had improved slightly, but icterus was still marked. The child took food more readily, and the urine was voided more frequently and in larger quantities. The baby seemed better, and from this time on the jaundice disappeared gradually. The baby nursed more normally and continued to improve. The child is now over a year old and seems unusually bright and happy, having had no illness of any consequence since then.

CONCLUSION

These reports relate the occurrence of a rare disease in new-born children, characterized by progressive icterus occurring in successive pregnancies and of unknown origin. The disease nearly always terminates fatally, though one of my patients recovered after a most serious attack and with the most alarming symptoms.[6]

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6. In addition to the references already given, the following will be found of interest:

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THE CALCIUM METABOLISM IN A CASE OF HEMOPHILIA*

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C. E., 9 years old, entered the hospital because of sudden enlargement of the right knee. He gave a history of repeated attacks of purpura, at times associated with vomiting and fever. The coagulation time of the blood was found to be two and one-half hours. Shortly after entrance he had a marked attack of purpura, with vomiting and fever; and during his stay in the hospital he had many spontaneous and subcutaneous hemorrhages. His brother, aged 19, was also under observation during part of this time for spontaneous hemorrhage into one knee.

A history of bleeding was obtained as follows: Of this family of twelve children, six girls and six boys, three of the boys were bleeders, one dying in infancy from hemorrhage. The maternal grandmother was a bleeder, and was one of ten children, four girls and six boys, three of whom were bleeders, herself and two brothers. The maternal great grandmother and her brother were the only bleeders in a family of seven children, five girls and two boys; her father (patient's great great grandfather) was a bleeder. Of the patient's family, in the order of birth, the third, fourth and eleventh male children were bleeders, the patient being the eleventh.

These data establish the case from the clinical side as one of hemophilia, with the characteristic transmission coming from the female side through two generations.

The coagulation time was determined by taking 3 c.c. of blood directly from a vein into a 10 c.c. test tube. It was placed in the incubator at 37 C. and carefully examined from time to time until the first definite appearance of clotting was observed (see table). During the control period the average coagulation time was two and one-half hours; during the third and fourth day of the calcium feeding period the coagulation time was lengthened two hours. The calcium content of the blood was increased over the control period at this time, as will be seen from the table. During the second control period, that is, after discontinuing the calcium, the coagulation time again returned to two and one-half hours.

The calcium determinations in the blood, urine, feces and food extended over a period of fourteen days. The patient was given a cathartic and put on a milk diet, 7 ounces (210 c.c.) accurately measured every two hours for eight feeds, or 56 ounces (1,680 c.c.) daily. The child was kept on this diet for two days before the determinations began.

H. Lyman's[1] turbidity method was employed for the calcium determinations. In the case of the feces, blood, and milk we substituted and adapted to our use an oxidation method in place of the incineration method usually used. This method was originated by Professor Willard of the department of chem-

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* From the Department of Pediatrics, University of Michigan Medical School.

1. Lyman, H.: Jour. Biol. Chem., 1915, **21**, 551.

istry for the estimation of the mineral content of coal and other organic material, the details of which are not yet published.

The first five days' determinations constitute the first control period, the following days the calcium feeding period, during which the patient received calcium lactate, as indicated in the table. Thirteen per cent. of calcium lactate is calcium. Twenty-six gm. of calcium lactate was to have been given dissolved in distilled water. This was equivalent to 3 gm. of calcium. After the first dose of 7 gm. of calcium lactate the patient complained of considerable epigastric pain, and vomited a small amount. The calcium had to be discontinued. On the seventh day 12 gm. of calcium lactate was to have been given in divided doses of 4 gm. each, but after the first dose the same symptoms recurred. The patient was then given a one-day period of rest from the lactate, during which the milk diet was continued. No determinations were made on this day.

CALCIUM DETERMINATIONS IN THE FOOD, URINE, FECES AND BLOOD

Day	Period	Food (Milk)		Urine			Feces		Calcium in 1,000 C.c. Blood, Gm.	Coagulation Time, H. M.
		Per Cent. Calcium	Total Calcium, Gm.	C.c.	Per Cent. Calcium	Total Calcium, Gm.	Weight, Gm.	Total Calcium, Gm.		
1	Control	0.343	5.0421	297	...	0.10048	32.01	0.5479	.....	....
2	.....	0.322	5.2245	1,030	...	0.482	.....	.....	0.6482	2:35
3	.....	0.344	5.3804	320	...	0.2322	.....	.....	0.6828	2:32
4	.....	0.329	5.3742	1,044	...	0.7471	128.6972	3.4045	0.66	2:48
5	.....	0.345	5.3944	832	8†	0.5578	.....	.....	0.6866	2:35
6	Calcium *	0.349	5.5522	545	...	0.3777	63.334	1.85644	0.6274	1:50
7	*	0.347	5.4256	545	...	0.3277	110.9778	2.4282	0.658	3:30
8	.....	.....	.....	.....	...	.....	.....	.....	.....	....
9	0.65 gm.	0.351	5.9085	744	...	0.5016	277.02	6.7102	0.665	3:00
10	0.91 gm.	0.343	5.4537	855	...	0.5021	.....	.....	0.6844	2:38
11	1.17 gm.	0.345	5.8111	635	...	0.4519	37.338	0.6372	0.7192	4:55
12	1.56 gm.	0.344	5.7926	942	1.5	0.6337	92.141	2.3703	0.7545	4:35
13	Control	0.344	5.7879	772	...	0.5241	260.1684	2.7117	0.6918	2:45
14	.....	0.345	5.8044	797	8	0.5102	99.875	1.814	0.6612	2:15

* The patient vomited the calcium lactate. The calcium was calculated as 13 per cent of the lactate.
† Percentage of total periods.

On the ninth day the patient was given 1 gm. of calcium lactate every two hours for five doses, which is equivalent to 0.65 gm. of calcium. On the tenth day 7 gm. of calcium lactate were given, 0.91 gm. of calcium. On the eleventh day 9 gm. of calcium lactate were given, 1.17 gm. of calcium; and on the twelfth day were given 12 gm. of calcium lactate, 1.56 gm. of calcium. This was followed by a control period of two days.

The accompanying table records the determinations made. The calcium content of the food (milk) was quite constant, as will be seen from the percentage of calcium in milk given in the table. It should be stated that these estimations make the calcium content of milk slightly higher than the figures usually given, which are from 0.149 to 0.198 per cent. The calcium content of the urine was apparently unchanged by the administration of calcium by the mouth. The blood calcium increased perceptibly but slightly during the calcium feeding period. The data obtained from the feces are of doubtful value, not because

of the method of analysis, but because of our inability to obtain daily stools on account of constipation, and because we erred in that we did not mark the stools. We hoped that the preliminary period of milk feeding before the estimations were begun and the long periods of control and of calcium feeding would enable us to obtain averages which would be of more value than one or two day observations. We were particularly interested in the blood calcium and these data, like those of the milk and urine, we believe are trustworthy and of value.

The following conclusions seem to be justified:

1. The calcium content of the blood in this case of hemophilia is the same as that obtained under normal conditions.

2. The calcium content of the blood increased perceptibly during the calcium feeding period.

3. The coagulation time of the blood was lengthened during the calcium feeding period.

4. The calcium content of the food (milk) was slightly greater in our series than in the usually reported analyses.

THE CEREBROSPINAL FLUID IN POLIOMYELITIS

WITH ESPECIAL REFERENCE TO THE LANGE REACTION *

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Early in poliomyelitis, before the onset of paralysis, or in those abortive cases which do not develop paralysis, there is found no pathognomonic diagnostic feature either at the bedside or in the laboratory. The clinical picture and history are usually fairly uniform and striking, but these same symptoms and signs are of such frequency in other infections that a reliable diagnosis cannot be made from them alone. The nearest evidence of a positive nature as to the presence of this infection in a preparalytic or abortive case is secured by the correlation of the clinical data with the results of examination of the cerebrospinal fluid.

The characteristics of cerebrospinal fluid in the early stages of poliomyelitis will be briefly summarized. It is clear and increased in amount. From 15 to 60 c.c. or more may be readily withdrawn. It frequently shows a marked web formation. The reduction of Fehling's solution is prompt, as in a normal fluid. There is a slight to moderate increase in the albumin, globulin and cellular elements. The cell counts vary from practically normal in a few cases to 500 or more per cubic millimeter, the majority having less than 200 cells per cubic millimeter. Eighty per cent. or more of these cells are mononuclears.

There are three rare types of cerebrospinal fluid found. One of these is a slightly cloudy fluid which shows a polymorphonucleosis, usually about 60 per cent., but which may be as high as 90 per cent. The other two types occur when the hemorrhagic process has been more than usually extensive. One of these has blood evenly diffused throughout the fluid, and the other, though having no blood cells, has a yellow color and coagulates spontaneously. The latter type has recently been present in our St. Louis material.

Conditions which may be confused with preparalytic or abortive poliomyelitis are *meningism, syphilis* and meningitis, either *tuberculous* or *purulent*.

In meningism is found a fluid increased in amount but normal in character, and the underlying infection is usually manifest after a short interval, if not at the first examination.

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In syphilis of the central nervous system there is usually found a fluid identical with that of poliomyelitis. However, in syphilis the fluid gives a positive Wassermann reaction and there is rarely if ever an acute onset with fever in children.

In purulent meningitis, even in the early stages, there is usually some degree of cloudiness from cellular increase and the cells are 90 per cent. or more polymorphonuclears. In certain mild cases of the epidemic variety the organism may never appear, but in the other varieties it will practically always appear, if not present at the first examination, as further punctures are made.

The differential diagnosis of poliomyelitis from tuberculous meningitis will often present difficulties. In both conditions the fluid is usually clear. The increase in the albumin, globulin and the cellular elements is usually greater in tuberculous meningitis than in poliomyelitis. The reduction of Fehling's solution is usually better in poliomyelitis, though many fluids from tuberculous meningitis reduce Fehling's solution readily, especially if obtained early in the disease. In both conditions there is usually mononucleosis, although in some cases of tuberculous meningitis there is a polymorphonucleosis. By careful search, tubercle bacilli may be found in 90 per cent. or more of fluids from tuberculous meningitis. In the remaining cases, animal inoculation and the clinical course of the disease must be depended on. Tuberculous meningitis seldom has the acute onset and high fever that accompany poliomyelitis. By correlating the laboratory findings with the clinical picture the differential diagnosis is usually not difficult, though several cases are recalled in which the diagnosis was later proved to be in error.

Since there is no one laboratory measure that is pathognomonic of this disease, it seems advisable to extend the laboratory examination as much as would prove helpful in arriving at a definite diagnosis. The Lange colloidal gold reaction has been observed by one of us on a small number of fluids from patients in cases of poliomyelitis occurring sporadically in St. Louis.[1] In these cases the occurrence of an early transitory reaction in the "syphilitic zone" in the acute stage suggested an important aid in the diagnosis. In order to study the reaction in a larger number of cases, Lange colloidal gold tests were made with fluids from patients in 100 cases occurring in the 1916 New York epidemic (Table 1).

Fifty-five of these patients had symptoms, including paralysis, which were sufficient evidence that they had poliomyelitis. In the fluids from the entire fifty-five there was definite reduction of the colloidal

1. Johnston, M. R.: A Study of Normal and Pathologic Cerebrospinal Fluids in Children, AM. JOUR. DIS. CHILD., 1916, **12**, 112.

gold solution with the lower dilutions of spinal fluid. This reaction occurred in a fairly uniform and regular manner, just as had happened previously in a smaller number of sporadic cases in St. Louis. In seven of these cases the Noguchi test gave a doubtful result (±) for globulin. In five of the seven there was no increase, or only very slight increase, in the cells. So that even in those cases of undoubted poliomyelitis in which there was apparently no change in the spinal fluid as far as the usual methods of examination show, the Lange test showed definite changes and was the only good evidence, aside from paralysis, that the cases were poliomyelitis.

The number of cases seen without paralysis, but which later developed paralysis, is not definitely known, but several are known to have progressed in this manner following the first lumbar puncture at which the material for this study was obtained, and in these cases the colloidal gold reaction was essentially no different in the pre-paralytic stage from that obtained after paralysis had developed.

Abortive cases which never become paralyzed are known to occur with considerable frequency. With the usual symptoms of onset and a cerebrospinal fluid that presents increased globulin and cells, a diagnosis of poliomyelitis is justified even in the absence of paralysis. In all such cases in this study the colloidal gold reaction was similar to that of the paralytic cases.

In cases presenting the usual symptoms of onset, not developing paralysis, and in which the cerebrospinal fluid showed no increase in the globulin, and slight or no increase in cells, but causing the usual colloidal gold reaction, it is to be concluded that these were cases of abortive poliomyelitis. It is in such cases that the Lange reaction shows its greatest usefulness. In this small series there were four such cases and two others having an increase in cells, but a doubtful globulin test. A Lange reaction is good evidence that a spinal fluid is pathologic and is sufficient to differentiate between poliomyelitis and meningismus or any other condition giving a normal cerebrospinal fluid.

The occasional difficulty of differentiating between a fluid from poliomyelitis and one from tuberculous meningitis is not made absolutely conclusive by the colloidal gold reaction. As is seen in the accompanying table (Table 2), fluids from cases of tuberculous meningitis cause the greatest changes in the middle dilutions, while the greatest changes caused by a fluid from poliomyelitis are in the lower dilutions. A distinct limitation of the maximum intensity to these zones is not constant in either condition. However, fluids from cases of poliomyelitis which cause a maximum change in the "Middle zone" at the same time produce changes in the lower dilutions — which is not the case with fluids from tuberculous meningitis. The variations in these reactions are so rare that we believe the colloidal gold reaction is

TABLE 1.—Results of Examination of Cerebrospinal Fluid in 100 Cases of Poliomyelitis *

No.	Lange Reaction	Albumin	Globulin (Noguchi)	Sugar (Fehling)	Cellular Increase†	Mononuclear, %	Amt., C.c.	Age, Years	Day of Disease	Remarks
2570	1112331000	++	+ 1	+++	Gt.	98	20	25	4	Paralysis of both lower extremities
2571	1123310000	++	++	+++	Mod.	70	10	32	4	Paralysis of left quadriceps and right leg
2573	1112200000	++	++	+++	No	..	35	5	19	Temperature 101 on day of admission, 14 days after onset;
2791	1122210000	+	+ 1	+++	Sl.	100	..	5	30	no paralysis
2574	1124300000	++	+ 1	+++	No	98	40	4	9	No paralysis; tenderness over spine; rigidity of back; temperature normal
2575	1122110000	+	±	+++	Sl.	98	30	4	13	No paralysis; temperature normal
2600	1221000000	+ 1	+ 1	+++	Sl.	95	25	Infant	8	
2760	1232120000	+ 1	++ 1	+++	Sl.	100	15	..	17	Weakness of muscles of shoulder, neck and back on right side
2601	1122110000	+ 1	++	+++	Sl.	95	25	3	8	Paralysis of right upper and both lower extremities; temperature normal
2602	1122200000	++	+ 1	+++	Mod.	98	25	..	13	Paralysis left deltoid; rigidity of neck
2610	1112100012	++	++	+++	Mod.	..	25	3	12	Temperature normal at time of puncture; no paralysis; had
2762	1233110000	+	+	+++	Sl.	100	10	..	21	a general tremor
2611	1221100000	++ 1	++ 1	+++	Mod.	90	30	2½	13	Temperature slightly elevated; Kernig and Macewen signs elic-
2765	1112220000	+ 1	++	+++	Sl.	..	15	..	22	ited; paralysis of left leg
2612	1122110000	++ 1	++ 1	+++	Sl.	..	10	2	12	
2764	1123331000	+ 1	++	+++	Mod.	100	12	..	21	Temperature normal; weakness of left quadriceps extensor
2614 ‡	1122100000	++	+	+	Mod.	90	..	1½	7	Child had never walked; had general weakness of long standing; hyperesthesia and general irritability at onset; high temperature on third and fourth days; no rigidity; Macewen sign doubtful; no paralysis
2615	1122210000	+	+	+++	Gt.	98	30	3	4	No paralysis; delirious; Macewen sign; tenderness along spine
2617	1112100000	++	++	+++	Gt.	98	12	6	6	No paralysis; temperature normal; clinically diagnosed "no
2780	1123210000	++	++	+++	Mod.	100	20	..	15	case"
2618	1123210000	++	+ 1	+++	Mod.	98	35	4	6	No paralysis; slight fever; weakness right leg 4 days later
2619	1123310000	+ 1	+ 1	+++	Gt.	99	15	3	9	Clinically diagnosed tuberculous meningitis; later appeared weakness of right shoulder; recovered
2623	1111000000	+	+	+++	Mod.	95	25	6½	4	Double ptosis; eye movements not coordinate; unable to swallow; weakness left deltoid, neck and back; diaphragmatic respiration. Died on fourth day
2625	1123210000	+ 1	+ 1	+++	Gt.	90	25	2½	3	Temperature 102; paralysis of both upper and lower extremities
2626	1123321000	+ 1	+ 1	++	Gt.	95	25	2	3	Paralysis of back, both deltoids and both lower extremities
2628	1122210000	+ 1	+ 1	++	Mod.	90	12	3	4	Died same day; diaphragmatic paralysis
2630	1123321000	+ 1	+	+	Mod.	95	12	6	7	Temperature normal; weak right arm and weak neck
2631	1121000000	+	±	+++	Sl.	90	25	1	3	Temperature 101; weak neck, back and deltoids; paralysis of quadriceps

2632	1123300000	+ 1	+ 1	+++	Mod.	90	18	1½	1	Temperature 103; developed paralysis of both legs
2633	0111100000	++	++	+++	Gt.	90	15	1½§	..	Paralysis both arms and legs, neck, back and right facial. Died third day
2634	1121000000	+	+	+	Gt.	90	12	4	3	Temperature 101; paralysis of left deltoid
2636	1122210000	++	+++	+++	Sl.	90	15	¾	2	Weak neck and back; paralysis of both legs
2639	0112210000	++	+ 1	+++	No	..	30	28	6	Temperature 100; previously higher; drowsiness; general weakness, especially of back; Wassermann reaction negative; clinical diagnosis, hysteria; five days later had Rombergism and weakness of right facial
2640	1122100000	+	+	+++	Sl.	90	15	..	..	Died; no paralysis; question of tuberculous meningitis
2641	1111000000	+	±	+++	Sl.	..	25	1½	4	No paralysis; onset with headache, vomiting, temperature 103; at time of puncture temperature 100, hyperesthesia, rigidity of neck; Macewen sign; tenderness over spine
2644	1121000000	+++	+++	+++	Mod.	95	12	3	4	No paralysis; onset sudden with temperature 103, headache and apathy; at time of puncture temperature 98.2; hyperesthesia; irritable; rigidity of neck; Macewen and Kernig signs elicited
2645	1122100000	+ 1	+ 1	+++	Gt.	90	35	2	2	No paralysis; onset with temperature 105; vomited once; at time of puncture slight rigidity of neck; hyperesthesia, tenderness over spine; Macewen
2646	1111000000	+	+	+++	Gt.	40	20	9	2	No paralysis; onset with temperature 103; vomiting and apathy; at time of puncture temperature 102; hyperesthesia; rigidity of neck; Macewen and Kernig signs positive
2647	1122100000	+	+	++	Mod.	95	20	3	6	Temperature 102.4; rigidity of neck and back; weak quadriceps; later thoracic paralysis
2648	1111000000	+	+	++ 1	Sl.	90	13	2	5	Paralysis left deltoid and both legs; later died of respiratory paralysis
2649	1122100000	+ 1	+ 1	++	Mod.	90	20	..	3	Paralysis both deltoids and quadriceps; temperature 101 to 104; later intercostal paralysis
2652	1121000000	+	+	++	Gt.	98	30	7	..	Probably poliomyelitis; no paralysis
2653	1111000000	+	±	+++	Mod.	90	30	2	..	Probably poliomyelitis; no paralysis
2654	2231000000	±	±	++	Sl.	95	10	2	5	Probably poliomyelitis; no paralysis; temperature normal
2655	1111100000	+	+	++	Mod.	98	..	6	3	Paralysis without previous illness
2661	1123110000	+	+	+++	Gt.	98	50	8½	5	Paralysis flexors left arm; rigidity neck and back; pain back and legs
2662	1121000000	+	+	+++	Gt.	95	..	7	1	No paralysis; fever, headache, vomiting; rigidity of neck
2664	1122110000	++	++	+++	Mod.	98	15	1½	7	Paralysis of right leg; temperature normal
2667	1111000000	+	+	+++	Sl.	95	25	2	16	Left facial paralysis; temperature normal; later right deltoid paralysis
2668	0125533510	++	++	+++	Gt.	99	20	2	2	Fever, stupor, tenderness over spine; later paralysis right leg and both arms
2669	1123332000	++	++ 1	+++	Gt.	98	..	5	3	Onset with temperature 103; vomiting and headache; rigidity of neck; temperature 101.2; partial paralysis both legs; irritable
2724	0123210000	+++	+++	++	No	..	..	..	6	
2677	2233310000	+++	++ 1	+++	Mod.	99	18	5	5	Temperature slightly elevated; paralysis of left leg

* For the nonparalytic cases in which information was obtainable there is appended a brief of the clinical data.

† The abbreviations denoting cellular increase indicate as follows: Sl. = slight increase, i. e., from 10 to 50 per c.mm.; Mod = moderate increase, i. e., from 50 to 150 per c.mm.; Gt. = great increase, i. e., above 150 per c.mm.

‡ 2614. Fluid from previous puncture bloody. This specimen shows a few red blood cells.

§ 2633. Age 1½ months.

TABLE 1.—Results of Examination of Cerebrospinal Fluid in 100 Cases of Poliomyelitis *—(*Continued*)

No.	Lange Reaction	Albumin	Globulin (Noguchi)	Sugar (Fehling)	Cellular Increaset	Mononuclear, %	Amt., C.c.	Age, Years	Day of Disease	Remarks
2678	1122100000	+	±	++	Sl.	100	7	2	2	Temperature 102; rigidity of neck and back; right facial paralysis
2679	2333233100	++ 1	++	+++	No	..	18	5/6	3	Temperature 101; paralysis both legs and left arm; died fifth day of respiratory paralysis
2680	1234310000	++	++	+++	Sl.	100	30	4½	2	Temperature normal; no paralysis; rigidity of neck and back; opisthotonus
2681	0112333111	+++	+++	+++	No	..	35	2	..	Rigidity neck and back; paralysis quadriceps and intercostals; died ninth day
2682	2333311000	+	+	+++	Mod.	100	35	3½	3	Onset with vomiting and temperature 102; left facial paralysis; Kernig; rigid neck
2683	1111100000	+ 1	+ 1	+++	Sl.	..	..	12	..	Clinical diagnosis, meningeal irritation due to injury; observed and punctured 8/16/16; had a fall 7/4/16; improved to two weeks ago when he began to feel bad again; much worse past few days; stuporous; Macewen and Kernig; clonus right ankle; on 10/14/16 report of complete recovery
2685	1112321000	++ 1	++ 1	+++	Mod.	95	35	1	7	Onset with gastro-enteritis; fever and prostration since; comatose; died seventh day of "respiratory paralysis"
2689	1122100000	+	+	++	Gt.	99	25	3¾	..	Paralysis both arms, legs, neck, voice and respiration; died sixth day
2695	1121100000	+	±	+++	Sl.	90	..	2½	3	Irritable; hyperesthesia; Macewen; questionable weakness right leg; (onset with temp. 103; headache, vomiting and apathy)
2696	1122200000	+	+	++	Mod.	98	..	2½	6	Temp. 102; hyperesthesia; increased reflexes; rigidity of neck; Kernig and Macewen positive; no paralysis; sudden onset with fever
2697	1112110000	+ 1	+ 1	++	Gt.	95	25	..	..	Clonic convulsions; probably poliomyelitis
2698	1222200000	++	+ 1	+++	Gt.	98	30	1½	7	No paralysis; temperature normal; neck rigid; Macewen positive; tenderness over spine; (sudden onset with temp. 103.5)
2703	1122110000	+	+	+++	Mod.	50	25	..	5	Paralysis; Macewen positive; died day of puncture
2704	1123220000	+	+	+++	Mod.	99	20		4	Moribund at time of puncture; died of respiratory paralysis
2705	1122210000	+	+ 1	+++	Sl.	98	15	..	4	Paralysis; died
2706	1122100000	+	+	+++	Gt.	100	20	..	8	Moribund; paralysis; died
2708	1122220000	+	+	+++	Mod.	100	15	..	3	Moribund at time of puncture; Macewen positive; reflexes absent; died
2715	±112330000	++	+++	+++	Mod.	100	..	..	2	Continued high fever; no paralysis; comatose; neck rigid; Kernig and Macewen positive; history of pertussis for two weeks; clinical diagnosis of tuberculous meningitis had been made; no tubercle bacilli found in fluid; died few hours after puncture
2717	1122100000	+	+	+++	Sl.	98	25	5/6	4	Temperature 101; paralysis of both legs
2718	1112331000	+	+	+++	Gt.	99	20	1/6	3	Temperature 100; rigidity of neck and back; question of anterior tibial paralysis
2720	1112331000	+++	++	+++	Sl.	100	12	¼	3	Died; paralysis respiratory muscles and of both arms and legs
2723	1233200000	+	+	+++	Mod.	99	30	3½	4	Fever; no paralysis; tremors and slight spasticity left leg
2725	1123331000	++	++	+++	Mod.	100	12	Adult	7	Paralysis of both legs
2729	1232200000	+	+	+++	Sl.	100	30	5	7	Temperature 99; left facial paralysis

2730	1133310000	+ 1	+ 1	+++	No	..	25	1¼	9	Paralysis left deltoid; (sediment shows slight blood)
2733	1123210000	++ 1	++ 1	+++	Gt.	98	40	13	5	Temperature 101; no paralysis; improving
2734	1122210000	+++	+++	+++	Sl.	100	40	3	21	Temperature 102 on third day; now stuporous; weakness right leg and right side of face
2738	1110000000	+	+	+++	No	100	30	..	..	No paralysis; question of poliomyelitis; had malaria
2740	0132200000	++	++	++	Gt.	100	20	8½	5	Onset with vomiting, headache and fever; temperature now 102; hyperesthesia; difficulty in swallowing; Macewen and Kernig signs positive
2741	1112100000	+	+	+++	Mod.	98	20	..	4	No paralysis; temperature 98.2; apathy; Macewen; rigidity of neck; onset with vomiting, headache and temperature to 102
2755	1233210000	+ 1	+ 1	+++	Gt.	100	25	10	1	Temperature 106; bulbar paralysis; delirium
2769	1122100000	+	±	+++	Gt.	100	25	..	4	Illness followed fall from window to floor; fall at 6:30 p. m.; vomiting in the night; fever next morning, with rigidity of neck and positive Kernig; increased reflexes; no paralysis
2770	1112210000	+++	+++	+++	Sl.	100	25	..	24	Paralysis of left arm and both legs
2771	1112320000	++	+ 1	+++	Sl.	100	15	23	43	Had facial paralysis for one day
2772	1232210000	+	+	++	Mod.	98	30	2	47	Paralysis of both legs; practically well
2773	1123100000	+	±	+++	Mod.	..	40	4	42	Full recovery; had weakness right leg and rigidity of neck and back
2774	1232210000	+	+	+++	Sl.	100	40	5	..	Paralysis left thigh, weakness of right; slight left foot drop; (discharged well eighth week)
2775	1111100000	+	+	+++	Mod.	..	10	6	47	Paralysis, left facial; tremors left thigh and both hands; complete recovery
2776	1123310000	+	+	+++	Mod.	100	..	..	11	Questionable poliomyelitis clinically; had chorea
2777	1122110000	+	+	+++	Gt.	100	20	..	..	Early cases at Queensborough Hospital; paralytic
2778	1123310000	++ 1	++ 1	+++	Mod.	100	18	..	..	
2779	2223110000	+	+	+++	Mod.	95	20	..	..	
2787	1112200000	+ 1	+	+++	Mod.	98	15	1	6	Temperature 100.8; no paralysis; Macewen positive; onset with vomiting and temperature 102
2788	1111000000	+	+	+++	Mod.	100	25	2	2	Temperature 100.8; no paralysis; Macewen positive tender spine; temperature at onset 104
2792	1132210000	+	±	+++	No	..	50	..	12	Paralysis of left leg
2793	1111100000	+	+ 1	+++	Gt.	98	30	..	..	Doubtful diagnosis clinically; question of typhoid
2794	1122200000	++	+	+++	Gt.	100	20	7	3	No paralysis; rigid neck; onset with vomiting, headache and temperature 104
2795	1123210000	++	++	+++	Mod.	99	50	1	4	Rigidity of neck; strabismus; Macewen; onset with vomiting and fever
2796	1112221000	++	++	+++	Mod.	99	40	4	4	No paralysis; irritable; hyperesthesia; rigid neck; tender spine; Macewen and Kernig positive; onset with vomiting and fever
360	1122100000	±	±	+++	No	..	25	..	2	Paralysis present
386	1121100000	+	+	+++	Sl.	98	10	..	2	No paralysis; (later had weakness of legs)
391	1112100000	+	+	+++	Sl.	98	25	..	4	Paralysis of right arm and leg
396	1233100000	+	+	+++	Mod.	97	15	..	17	Left facial paralysis
401	±112100000	+	±	+++	Mod.	98	..	..	17	Paralysis present

a distinct aid in the differentiation of these two conditions, before the clinical picture is entirely clear.

Products in the cerebrospinal fluid of a purulent process in the brain or meninges cause colloidal gold changes in the higher dilutions, thus being quite different from the changes produced by a fluid from poliomyelitis. The other cerebrospinal fluid changes resulting from the various purulent infections, however, are usually such that a Lange test is quite unnecessary.

TABLE 2.—A FEW SELECTED TESTS IN TUBERCULOUS MENINGITIS AND POLIOMYELITIS SHOWING THE USUAL REACTIONS AND THE EXTREME VARIATIONS

Tuberculous meningitis	Poliomyelitis
±±12442±00	1123321000
±±1332±000	1123331000
±±±2555100	1112320000
±12444±000	1112331000
±24422±000	1122100000
0002332000	1123210000
00±553±000	1221000000
0003444000	1121000000
1114444100	

SUMMARY

The colloidal gold reaction with cerebrospinal fluid from patients with poliomyelitis has been recorded in isolated instances, and by one of us in a small number of sporadic cases occurring in St. Louis. The results in these few cases indicated that this reaction might be of service in the diagnosis of this disease. In order further to investigate this point, cerebrospinal fluids from patients in 100 cases occurring in the recent New York epidemic were examined, and it is the object of this paper to record the results.

From these results it is to be concluded that the colloidal gold reaction is of distinct service in the diagnosis of poliomyelitis. The greatest usefulness of the reaction is in showing to be pathologic a fluid which does not give other evidence of abnormality when examined as to its albumin, globulin and cellular content. This evidence of abnormality is most useful in those cases of poliomyelitis in which there are the usual symptoms of onset and in which paralysis has not developed. It is also our belief that the Lange reaction is of service in differentiating between poliomyelitis and tuberculous meningitis, between which diseases there not infrequently arises for a time a confusion as to diagnosis.

THE SCHICK TEST IN POLIOMYELITIS, SCARLET FEVER, MEASLES AND IN NORMAL CHILDREN

ITS BEARING ON THE QUESTION OF NATURAL IMMUNITY *

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The routine employment of the Schick test in children with poliomyelitis admitted to the Willard Parker Hospital during the recent epidemic established a most interesting and significant fact. This, in conjunction with some previously published observations on the Schick reaction in normal children and in children suffering from scarlet fever, and some more recent observations with the test in cases of measles, may throw some light on the still open question of natural immunity and suceptibility of individuals to infectious diseases.

From a previous communication on the Schick reaction[1] the accompanying tables (Tables 1 and 2) are taken.

TABLE 1.—SUMMARY OF SCHICK TESTS IN 2,700 NORMAL CHILDREN

Age, Years	Total	Negative Schick	Positive Schick	Per cent. Positive Schick
2 to 4	62	42	20	32.2
4 to 6	318	236	82	25.7
6 to 8	444	347	97	21.8
8 to 10	597	462	135	22.6
10 to 12	584	459	125	21.4
12 to 14	506	416	90	17.7
14 to 16	189	158	31	16.4
	2,700	2,120	560	21.4

The tables show the results obtained with the test on a large series of normal children and scarlet fever patients. It is interesting to note that normal children between the ages of 2 and 4 years show about 32 per cent. of positive reaction, as compared with scarlet fever patients, of whom about 65 per cent., or more than twice as many children, gave a positive reaction.

* Submitted for publication Dec. 23, 1916.

* From the Department of Health, City of New York.

1. Park, W. H., and Zingher, Abraham: Diphtheria Immunity. Its Determination by the Schick Test, Am. Jour. Pub. Health, 1916, **6**, 431.

TABLE 2.—Schick Reactions Among Scarlet Fever Patients

Age, Years	Total	Negative Schick	Positive Schick	Per cent. Positive Schick
½ to 1	10	5	5	50.0
1 to 2	68	22	46	67.6
2 to 4	223	93	180	65.9
4 to 6	249	116	133	53.4
6 to 8	196	123	73	37.2
8 to 15	237	171	66	27.8
Over 15	167	126	41	24.5
	1,200	656	544	45.3

TABLE 3.—The Schick Test in Measles Cases

Age, Years	Total	Negative Schick	Positive Schick	Per cent. Positive Schick
Up to 1	35	25	10	28.6
1 to 2	53	35	18	34.0
2 to 4	64	37	27	42.1
4 to 6	44	29	15	34.0
6 to 8	17	14	3	18.2
Total	213	140	73	34.2

Table 3 gives the results with the Schick test obtained in a series of 213 cases of measles. This table shows that between the ages of 1 and 4 years only about 10 per cent. more of the children gave a positive reaction than normal children of the same age group.

Table 4 shows the results with the Schick test in 1,350 poliomyelitis cases. Between 1 and 4 years of age there is an average of over 80 per cent. of positive reactions. This percentage is based on over 1,000 cases and can, therefore, be accepted as being fairly accurate. It was interesting and striking to see in the wards of the Willard Parker Hospital row after row of children who gave a positive Schick reaction. Indeed, at one time the number of positive tests in this age group reached between 90 and 95 per cent.

What are the significant facts to be found in the four tables? They give the results of tests in fairly large series of cases and are, therefore, probably correct. Such a preponderance of individuals susceptible to diphtheria among cases of poliomyelitis and scarlet fever suggests one of two possible causes:

TABLE 4.—The Schick Test in Poliomyelitis Cases

Age, Years	Total	Negative Schick	Positive Schick	Per cent. Positive Schick
Up to ¼	11	9	2	18.2
¼ to ½	30	20	10	33.3
½ to 1	150	32	118	78.7
1 to 2	529	92	437	82.6
2 to 4	425	88	337	79.3
4 to 6	122	42	80	65.6
6 to 8	42	19	23	54.8
8 to 10	16	11	5	31.3
10 to 15	7	4	3	42.9
Over 15	18	12	6	33.3
Total	1,350	329	1,021	75.6

1. A destruction of the natural diphtheria antitoxin content during an attack of poliomyelitis or of scarlet fever. In order to explain the greater prevalence of diphtheria among scarlet fever children, von Behring[2] and others have suggested that there is a temporary loss of the natural immunity to diphtheria during the acute febrile stage of the disease. This loss is caused, according to v. Behring, by a destruction of the small amount of natural antitoxin present in some individuals, which is just sufficient to give a negative Schick test. This destruction of the natural antibody content during an acute infectious disease has been claimed for measles as well as for scarlet fever. Karasawa and Schick,[3] however, have shown that in measles the natural antitoxin content in normal children, and later in the same children during an attack of measles, was approximately the same, thus demonstrating that there is no excessive destruction of antibodies against diphtheria during the febrile stage of measles. We had the opportunity of making an interesting observation bearing on this question in cases of scarlet fever and poliomyelitis. Some of the children suffering from these diseases, who gave a positive Schick test on admission to the hospital and were not immunized either actively or passively against diphtheria, continued to show a positive reaction during their entire stay in the institution, which varied from six to eight weeks. If the positive Schick reaction had indicated only a temporary loss of

2. Von Behring, E.: Ueber ein neues Diphtherieschutzmittel, Deutsch. med. Wchnschr., 1913, **39,** 873.

3. Karasawa, M., and Schick, B.: Ueber den Gehalt des Serums diphtherie und masernkranker Kinder an Schutzkörper gegen Diphtherietoxin, Jahrb. f. Kinderh., 1910, **72,** 460.

the natural antitoxin during the febrile stage of the disease, then these antibodies would have rapidly reformed during convalescence and the retest with the Schick reaction would have been negative. The continued positive reaction rather points to the following possibility:

2. *A susceptibility to one of the less contagious diseases indicates that the child is also more apt to be susceptible to other contagious and infectious diseases.* From the little that is known of the infectiousness of poliomyelitis, we have in it a disease which is, according to Frost,[4] only one-fifteenth as infectious as scarlet fever. We would expect, therefore, that the relatively small proportion of children who are susceptible to poliomyelitis would be also more apt to be susceptible to diphtheria than children suffering either from scarlet fever or measles. Again, since scarlet fever is only about one-fourth as contagious as measles, we would also expect more scarlet fever than measles patients to be susceptible to diphtheria. In measles, on the other hand, we have, according to Herrman,[5] a disease which is almost universally contagious (96 per cent.) for children between the ages of 1 and 4 years. We would, therefore, expect to find in patients with measles the same, or only a slightly larger, number of children susceptible to diphtheria (positive Schick reactions), as in normal children. The four tables give rather strikingly corroborative proof of the probable correctness of this view.

These results do not, of course, explain the underlying and all-important question relating to the cause and nature of the so-called natural immunity. They lead, however, to the following suggestions:

1. Natural immunity can be best studied in a disease like diphtheria, for which we have a natural antibody that can be exactly measured in the animal test[6] and clinically determined by the Schick test.

2. The presence or absence of natural immunity, as shown by the Schick test, could be profitably studied in its relation to the Mendelian law. By making careful observations on a larger series of families, on the children as well as on their parents and possibly grandparents, some of the laws controlling the hereditary character of natural immunity might be revealed. To avoid errors, a history of diphtheria, or the recent administration of antitoxin, should always be carefully inquired into and noted with each individual.

We drew attention in our very first communication[7] to the fact that

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4. Frost, W. H.: Epidemic Poliomyelitis. What Is Known of Its Cause and Modes of Transmission, Pub. Health Rep., 1916, **31,** No. 28.

5. Herrman, C.: The Communicability of Acute Poliomyelitis; Its Spread and Control, Am. Med., 1916, **11,** 713.

6. Zingher, A.: A Modification of Roemer's Intracutaneous Method for the Determination of Small Amounts of Diphtheria Antitoxin in Blood Sera, Jour. Infect. Dis., 1916, **19,** 557.

7. Park, W. H., Zingher, Abraham, and Serota, Harry M.: The Schick Reaction and Its Practical Applications, Arch. Pediat., 1914, **31,** 481.

there is a probable hereditary element in the natural immunity against diphtheria. By natural immunity is not meant the short immunity present during the first few months of an infant's life. This immunity is only a temporary passive protection caused by the presence of antitoxic antibodies which are probably derived through the placenta from the mother's circulating blood. We pointed out that there is a distinct relationship and grouping among children belonging to the same family: (a) that the Schick test applied to the children in one family would be frequently either uniformly positive or negative in all; (b) where variations existed in the test, the older children generally gave the negative, the younger ones the positive reaction; (c) where the youngest child, if more than 2 years old, gave a negative Schick test, then the older children generally also showed a negative test. This interesting phenomenon, of course, pointed either to living under the same conditions of environment and the development of an immunity due to similar exposures, or else to an inherited family tendency to acquire early in life a natural immunity. This latter view is probably corroborated by the following observation: (d) Where the oldest child in a family gave a positive reaction, the younger children, with very few exceptions, also gave positive Schick reactions. It is difficult to conceive that in these families some of the older children had not been exposed, and probably frequently exposed, to infections with the Klebs-Loeffler bacillus. This can, therefore, only be explained by the absence of an inherited ability to develop an early immunity to diphtheria.

SUMMARY AND CONCLUSIONS

1. The Schick test is positive between 1 and 4 years of age in about 32 per cent. of normal children, in a slightly larger proportion of cases of measles, in twice as many cases of scarlet fever and nearly three times as many cases of poliomyelitis.

2. Susceptibility to one of the less contagious diseases, like poliomyelitis, indicates that the child is more apt to be susceptible to other contagious and infectious diseases.

3. Natural immunity reveals interesting problems, which can be partly solved by a study with the Schick test in diphtheria immunity.

4. A uniform technic of making the test, standard solutions of toxin, a uniform interpretation of the test, and a large series of cases are essential in any attempt at making important deductions from the results obtained with the Schick reaction.

CLINICAL DEPARTMENT

A CASE OF DIAPHRAGMATIC HERNIA*

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History.—Baby G., 3½ months old, came under my care Oct. 6, 1916, with a history of recurrent attacks characterized by extreme cyanosis, dyspnea, and, judging from his hard crying, severe pain, the condition being relieved by a movement of the bowels or by the expulsion of gas, sometimes in large quantities.

His birth history was unimportant, and for two weeks he seemed a normal baby. The attacks were then first noted, and gradually increased in severity and frequency, until, of late, dyspnea had been more or less persistent, with several daily exacerbations of symptoms. The present attack had continued some forty-eight hours, with but little remission, and was the worst yet experienced.

Examination.—Examination showed a well developed, moderately well-nourished boy baby. He appeared practically moribund, being cold and cyanotic, and evidently suffering most extreme respiratory embarassment, there being violent recession of the lower chest wall at each inspiratory effort, with but little apparent intake of air, as though there were a laryngeal or tracheal obstruction. The throat was clear. On percussion of the chest, the left side gave a curious impression of hollowness, not exactly tympanitic in quality. The heart was found far over on the right side, and its action was very labored. Breath sounds were audible only over the upper portion of the right chest, none being heard on the left. The abdomen was much retracted.

Stimulation and the free administration of oxygen revived the baby, and a roentgenogram was taken, showing the presence of gas in the left side of the thorax (Fig. 1).

A diagnosis was made of probable diaphragmatic hernia, and this was confirmed by a roentgenogram taken after a barium enema (Fig. 2), in which the colon is seen within the chest cavity.

To determine the extent of the hernia, a barium meal was given and serial roentgenograms taken (Figs. 3 to 8), showing almost all the intestine above the diaphragm.

By more or less constant administration of oxygen, and routine washing out of the bowel, the baby was kept fairly comfortable for several days, but in view of the condition disclosed by the roentgenograms, it was manifestly impracticable to continue this treatment indefinitely.

It was therefore decided to open the abdomen on the bare possibility that an operable condition might be found, and this was done by Dr. L. P. Adams, October 13.

Operation.—The defect in the diaphragm was found to be an oblique slit about 1 inch long between the muscle fibers close to the point of penetration of the great vessels and esophagus. Through this the intestine was withdrawn and replaced in the abdomen, and the defect readily closed by sutures. The baby, however, survived the operation only a few hours.

COMMENT: A physician who had seen the baby from birth, and who had last examined it some two weeks before it came under my

* Submitted for publication Dec. 10, 1916.

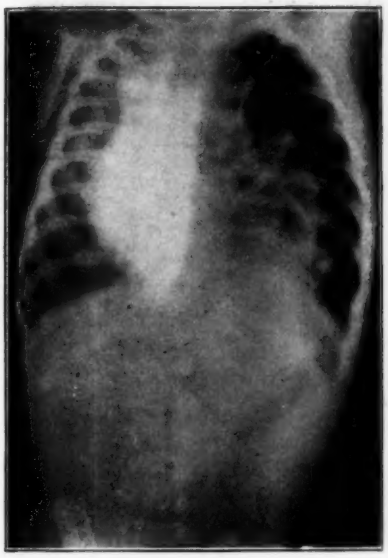

Figure 1

Figure 2

Fig. 1.—Author's case of diaphragmatic hernia, showing the presence of gas in the left side of the thorax.

Fig. 2.—Roentgenogram taken after barium enema, showing the colon within the chest cavity.

Figure 3

Figure 4

Fig. 3.—Roentgenogram taken fifteen minutes after barium meal, showing almost all of the intestine above the diaphragm.

Fig. 4.—Taken one hour after barium meal.

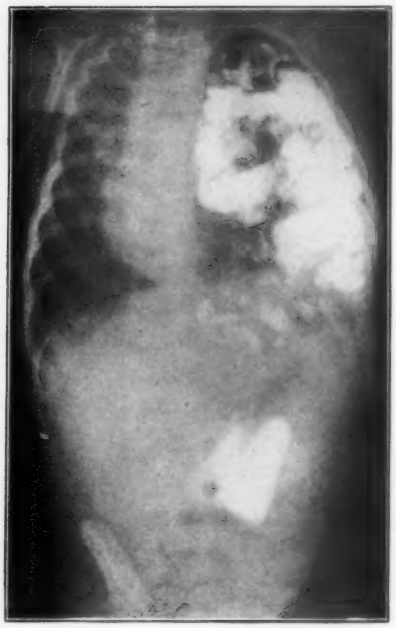

Figure 5 Figure 6

Fig. 5.—Taken two hours after barium meal.

Fig. 6.—Taken three hours after barium meal.

Figure 7 Figure 8

Fig. 7.—Taken five hours after barium meal.

Fig. 8.—Taken eight hours after barium meal.

observation, declared that he did not then or previously note the cardiac displacement and absence of breath sounds, and he believed that these signs developed later. The history of gradual increase, with recent very marked exaggeration of symptoms would also indicate that the herniation of the bowel into the thorax had been progressive. The defect itself, as disclosed at operation, was readily amenable to surgery, but the necessary handling, inch by inch, of the entire intestine at this time produced a degree of shock which could not be tolerated by an infant already weakened and worn out by many weeks of precarious struggle for breath. Had there been but little intestine to handle, as would have been the case in early operation, there would have been reasonable expectation of recovery.

A history of dyspnea and cyanosis, otherwise unaccounted for, especially if relieved by the passage of gas and feces, should excite suspicion of diaphragmatic hernia, and Roentgen-ray examination should be promptly resorted to, since this affords so ready and definite a means of diagnosis. This case demonstrates that the degree of herniation of the bowel is no criterion of the extent of the defect in the diaphragm, and would seem to suggest the propriety of early operation in all such cases.

I am indebted to Mr. P. L. Ansel for the excellent Roentgen-ray plates.

Federal Realty Building.

PROGRESS IN PEDIATRICS

RÉSUMÉ OF WORK ON TUBERCULOSIS IN CHILDREN FOR 1916

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CHICAGO

MODES OF INFECTION

1. Von Weller, C.: Two Additional Cases of Miliary Tuberculosis of the Placenta with Clinically Latent Tuberculosis of the Mother, Arch. Int. Med., 1916, **17,** 509.

2. Ravenel, M. P.: Present Views in Respect to Modes and Periods of Infection in Tuberculosis, Jour. Am. Med. Assn., 1916, **66,** 613.

C. von Weller[1] reports two cases of miliary tuberculosis of the placenta, with clinical latent tuberculosis of the mother. He calls attention to the fact that the reported cases of placental tuberculosis may be arranged in three groups.

1. Cases in which the mother was known to be tuberculous and in which, as a result of this knowledge, the placenta was given intensive study and found to exhibit the characteristic lesions of tuberculosis, either with or without a demonstration of the bacilli.

2. Cases in which the mother was known to be tuberculous, and in which the presence of tubercle bacilli in the placenta or fetal blood was demonstrated by staining methods or by animal inoculation without the recognition of tuberculosis of the placenta.

3. Cases in which the maternal tuberculosis was clinically unrecognizable and in which characteristic histopathologic lesions of tuberculosis were found in the routine examination of placentas. In this group fall the two cases forming the subject of this report, also one other case previously reported by Dr. Warthin.

The first case was that of a woman of 21. On entrance to the obstetric service, April 23, 1914, no signs of pulmonary lesions were discovered, and on June 11 she was delivered of an apparently healthy child. The placenta was sent to the pathologic laboratory and in the course of the routine microscopic examination miliary tubercles were found. Eighteen months after the birth of the child both mother and child were under observation, were apparently well, and had given no evidence of tuberculosis at any time.

The second case was that of a woman of 27. She wilfully falsified in regard to her history in order to conceal an earlier diagnosis of tuberculosis. Examination revealed no signs of tuberculosis. She was delivered of an apparently healthy child Feb. 4, 1914. On routine

examination of the placenta there was found a group of four or five miliary tubercles. The patient remained well for seventeen months after the birth of the child, except for some cough and sputum. She then developed well-marked signs of the disease.

That three such cases should be found in one laboratory and within the space of three years is strong argument, not alone for the belief that the maternal transmission of tuberculosis is much more common than is ordinarily thought, but also for the little recognized fact that a "subclinical" tuberculosis may be so influenced by pregnancy that the bacilli may enter the blood stream and produce placental or fetal miliary tuberculosis.

M. P. Ravenel[2] outlines the present views in respect to modes and periods of infection in tuberculosis. He says the evidence at hand indicates that in the majority of cases the respiratory tract is the route of infection. The work of Arnold and the experiments of Cornet are mentioned as furnishing the basis for this belief. Further evidence seemed to be at hand in the greater number of cases in which the supposedly primary lesion was found in the lungs and bronchial lymph glands as compared with the intestine and mesenteric glands. The value of this evidence, however, has been weakened during recent years by the discovery of the fact that in children the bronchial lymph nodes are often tuberculous, when no changes can be found in the lung; and the belief is growing that the lymph glands are first infected and the lung tissue involved later. Ravenel thinks, moreover, that the fixing of the portal of entry by the so-called oldest lesion is open to serious question. He has produced fatal pulmonary tuberculosis in monkeys by feeding tubercle bacilli. The oldest lesions were in the lungs and bronchial glands, yet the method of feeding precluded the possibility of the tubercle bacilli reaching the lungs except through the digestive tract. Practically all observers agree that in children there is a marked tendency to rapid and general dissemination of the disease, and many note that it is frequently impossible to determine the oldest lesion.

The alimentary tract is, according to Ravenel, a very frequent portal of entry for the tubercle bacillus, especially in children. The tubercle bacillus is able to pass through the intact mucous membrane of the alimentary tract without producing a lesion at the point of entrance. This takes place most readily during the digestion of fats. The bacilli pass with the chyle through the lacteals and thoracic duct into the blood, which conveys them to the lungs, where they are retained largely by the filtering action of the tissues.

The frequency of infection through the tonsil has been recently called in question by von Pirquet, and the evidence that the tonsils are often the portal of entry for the tubercle bacilli appears to the

writer very conclusive, while it seems equally certain that food is the bearer of the infection in a large proportion of cases.

Infancy and childhood are preeminently the periods of life when the individual is susceptible to tuberculous infection, and infection occurs chiefly during these early years. Tuberculous infection in adult life occurs, but not so frequently or readily as is generally believed. A campaign against tuberculosis which leaves out of consideration the protection of children against infection will fail.

BACTERIOLOGY

3. Eastwood, A., and Griffith, F.: The Characteristics of the Tubercle Bacillus in Human Bone and Joint Tuberculosis, Jour. Hyg., 1916, **15,** 257.

4. Marfan, A. B.: Pathogenic Micro-organisms in Milk, Le Nourrisson, 1916, **4,** 34.

5. Beattie, J. M., and Lewis, F. C.: Successful Destruction of Tubercle Bacilli in Milk by Electricity, Brit. Jour. Tuberc., 1916, **10,** 23.

6. Beattie, J. M., and Lewis, F. C.: Successful Destruction of Tubercle Bacilli in Milk by Electricity, Jour. State Med., 1916, **24,** 174.

A. Eastwood and F. Griffith[3] have studied the bacteriology in 261 cases of bone and joint tuberculosis. Material used in their investigation was removed directly from an affected joint or bone, or from an abscess in the neighborhood of such a lesion. The bacilli isolated were described as the bovine or human type, or as atypical. From the 261 cases the human bacillus was isolated in 196 instances, the bovine in fifty-five, and the atypical forms in ten. In studying the age incidence of those infected by the bovine type, the authors found that in 155 cases of children under 10 years of age, forty-five, or 29 per cent., showed the bovine type of bacillus; in 106 cases of children over 10, only ten, or 9 per cent., showed the bovine type, and among forty-four over 16 years there were only three cases of bovine type.

In regard to the possibility of tubercle bacilli occurring in milk, A. B. Marfan[4] says that only exceptionally have they been found in human milk. A few experimenters have produced tuberculosis in animals by injecting them with the milk of tuberculous women. Marfan says that there are only two authentic reports of infants being infected by the milk of the mother. These were cases of Demme and Roger and Garnier. It is, however, necessary to interdict breast-feeding by all women afflicted with pulmonary tuberculosis. On the one hand, nursing lowers the mother's nutrition, and, on the other, the child receives an insufficient amount of milk, charged with toxic products, although it may not contain virulent bacilli. Moreover, a child nursing from a tuberculous mother runs the risk of being contaminated by the sputum, because of the intimate relation between nurse and babe.

Certain facts have been well established in regard to the transmis-

sion of tubercle bacilli by cow's milk. It has been demonstrated that cow's milk often contains living and virulent tubercle bacilli. In the milk of cows afflicted with mammary tuberculosis these bacilli are very abundant, and, contrary to what has been admitted previously, milk of cows, healthy in appearance and not presenting appreciable clinical evidence of disease of the mammary gland, may also contain virulent bacilli. This is true of the milk of any animal which has reacted to an injection of tuberculin. Virulent bacilli are also present in milk products, cheese, cream, and butter, and it seems that butter, considered less dangerous than milk, is often richer in virulent bacilli.

Milk may become infected by bacillary excrements after being milked. The fecal matter of tuberculous animals is often rich in bacilli; excrements soil the walls of the stables, the bed, and external parts of the animals, the hands of the milkers; dried, they penetrate the atmosphere and are scattered broadcast.

Milk infected with the tubercle bacillus may cause cervical adenitis in children, but more often tuberculosis of the mesenteric glands. The frequency of alimentary tuberculosis in the first years of life, then, can give an approximate idea of the frequency of infection from milk. Statistics extending over fifteen years have shown that alimentary tuberculosis occurs in children, especially from 2 to 5 years of age, and that it comprises 8 per cent., of all cases of tuberculosis observed. Today this proportion has diminished, notably because of better oversight of infected animals and of the general use of sterilized milk.

Marfan summarizes his paper as follows: As cows are often tuberculous, and, when they are, their milk is infectious, and as the ingestion of infectious milk can produce disease not only in animals but also in human beings, especially among the young, means must be taken to prevent this mode of infection. At present the boiling of milk seems to be the most practical preventive measure.

J. M. Beattie and F. C. Lewis,[5] completing a series of experiments on the treatment of tuberculous milk with electricity, think they have fully established the claims that this is efficient for the total destruction of the bacillus of tuberculosis in a milk supply. Injection into guinea-pigs of naturally occurring tuberculous milk, and of artificially infected milk, proved that the bacilli had been destroyed.

While in a later article the writers[6] say that more recent experiments would at first sight seem to suggest that the method is not wholly dependable, they conclude as follows: "Experiment seems to confirm our former opinion that this plan can be worked successfully, but there must be strict adherence to certain definite conditions of measurement, rate of flow, current density, etc., and further experiments are necessary to establish the relation of these conditions to one another."

SYMPTOMATOLOGY

7. Combe: Clinical Forms of Tuberculosis in Childhood, Le Nourrisson, 1916, **4,** 73.
8. Combe: Generalized Forms of Tuberculosis in Infants, Le Nourrisson, 1916, **4,** 155.
9. Koch, H.: Tuberculosis in Infancy, Ergebn. d. inn. Med. u. Kinderh., 1915, **14,** 99.
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25. Little, G.: Acute Disseminated Tuberculosis Cutis, Brit. Jour. Child. Dis., 1916, **13,** 305.
26. Little, G.: Lichen Scrofulosorum, Brit. Jour. Child. Dis., 1916, **13,** 305.
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Combe[7] divides the clinical forms of tuberculosis into two groups. In the first group he places localized, and in the second generalized forms. Of the localized forms, he distinguishes, (1) larval tuberculosis, (2) suspected tuberculosis, (3) tuberculosis masked as dyspepsia, (4) tuberculosis masked as anemia.

The only manifestation of the larval form is a positive Mantoux reaction detected in the routine examination of infants for causes other than tuberculosis. Radioscopic examination of the chest then reveals shadows indicative of enlarged tracheobronchial glands, and careful physical examination, areas of dulness or modified respiratory or voice sounds.

In the suspected form the infants have a tuberculous heredity and are below normal in weight and appearance. The Roentgen ray shows a more or less suspicious shadow. The von Pirquet or the Mantoux test is at first negative but, if repeated every fifteen days, it becomes positive.

The masked forms are the most important and are the result of the action of the tuberculotoxins. According to some writers, and Combe agrees with them, the tuberculotoxins act on the nervous system of infants, as of older children, and cause a decided change of character. The infant loses its gayety; it never smiles, but cries without cause. It sleeps badly, awaking often, but is difficult to arouse in the morning. The two characteristic effects of the tuberculotoxins, however, are the destructive action on the digestive ferments and the hemolytic action, giving rise to the dyspeptic and anemic forms of tuberculosis.

Combe found that in 85 per cent. of older tuberculous children the tuberculotoxins acted on the gastric glands and caused a lessened secretion of pepsin and hydrochloric acid. In infants this destructive action appears even more general and gives rise to a dyspepsia and consequent atrophy. In the dyspeptic stage the child is pale and emaciated, has slight appetite, and at the end of the meal regurgitates the food. Colic is a frequent symptom, the abdomen is tense because of gas, the stools are pale yellow, sometimes contain mucus, are acid in reaction, and have an odor of butyric acid. The infant is cross, restless, sleeps badly and has a slight fever.

In the atrophic stage, the emaciation is extreme. The child has the features of a little old man, with wrinkled, yellow, dry skin and thin extremities. In grave cases this appearance is accompanied by a hypothermia, irregular respiration, and concentration of the blood, shown by an increase in the number of red blood cells (6,000,000) and hemoglobin (150 to 160 per cent.). These symptoms of the dyspeptic and atrophic form do not differ essentially from the symptoms of other organic dyspepsias and atrophies, but careful examination often reveals other signs of tuberculosis, such as "facies vasodilatation," micropolyadenitis, macropolyadenitis, and hypertrophy of the spleen and liver. Of these the most important is the macropolyadenitis, which is characterized by the presence of many glands, the size of a pea or nut, in the subclavicular spaces, in the thoracic wall or in the abdominal wall, glands communicating with the pleura or peritoneum and having the same diagnostic significance for tuberculosis which enlargement of the epitrochlear glands has for syphilis. In order to establish a positive diagnosis of tuberculosis, however, all these signs must be confirmed by local signs of tracheobronchial adenopathy and by the Mantoux tuberculin test.

The form masked as anemia is more rare than the preceding, and gives rise to three clinical pictures: (1) that of a simple anemia, with a moderate diminution of red blood cells and hemoglobin and no microscopical changes; (2) that of an anemia pseudoleukemia, with diminution in the number of red blood cells and hemoglobin and disturbance in the hemolytic function of the bone marrow, which causes the blood stream to be flooded with red blood cells of all ages, normoblasts, macrocytes, myelocytes and myeloblasts; (3) the picture of a pernicious anemia, with considerable diminution of the red blood cells and a marked diminution in the percentage of hemoglobin, and a color index of plus one. The microscopic examination of the blood shows an almost normal condition, except for the large number of macrocytes and gigantoblasts. The appearance of infants with the masked anemia differs little from those with essential anemias. The chief difference is the redness of the lips, due to vasodilatation, in striking contrast to the pallor of the face.

These evidences of tuberculosis lead to a search for tracheoadenopathy by physical examination and roentgenoscopy. Prevertebral signs of enlarged glands, as dilated veins over the vertebrae, spinalgia, exaggerated voice and breath sounds heard below the fourth dorsal vertebra, and prevertebral dulness, are of questionable value in infants, and in any case can be relied on only when very apparent. Intervertebroscapular signs are more important. Thoracic vibrations are clearly increased in the lateral vertebral regions, if there is a mass of glands to transmit the sounds. Dulness in this region is a salient sign. A vesicular murmur on one side and bronchovesicular or bronchial murmur on the other are very conclusive. A diminution of the respiration on the same side as the dulness and bronchovesicular breathing indicate a compression of the bronchus by enlarged glands. However, as in the prevertebral signs, these must be very apparent in order to have diagnostic value.

Roentgenoscopy has become the best means of detecting enlarged tracheobronchial glands in infants, but considerable experience is necessary to interpret properly a roentgenogram of the thorax.

Combe[8] classifies the generalized forms of tuberculosis according to the mode of extension of the disease. In the first group he places the forms resulting from extension through the lymphatics, in the second those from extension by means of the bronchi, and in the third those from extension by means of the blood vessels.

He describes two forms resulting from extension through the lymphatics, namely, generalized and localized glandular tuberculosis. In the generalized form there is an involvement of all the glands of the body. At necropsy, masses of glands are found surrounding the bronchi and in the mesentery, and large solitary tubercles in the spleen,

liver and kidney, but no generalized tuberculous infiltration of the viscera. Clinically, there is present the condition which Combe has previously described as "athrepsia vasodilatation." There is also marked pallor, a peripheral micropolyadenitis, and enlarged liver and spleen. But most characteristic are the masses of palpable glands in the subclavicular spaces, in the abdomen and in the iliac fossae. The Roentgen ray shows a definite enlargement of the bronchial and hilus glands, examination of the blood a leukopenia and a lymphopenia.

The localized glandular forms Combe designates as "hilus tabes" and "tabes mesentericus." In the first stage of hilus tabes the tuberculous process remains limited to the tracheobronchial glands; in the second stage it extends beyond the capsule of the glands into the pulmonary parenchyma. Separate tuberculous foci fuse and involve large areas of lung into a homogeneous mass. Clinically, these masses give the impression of a tumor, and the author prefers the name of pulmonary tuberculoma to tuberculous pneumonia, as it better indicates their hard, firm, homogeneous character, with absence of softening, and as it explains more satisfactorily the physical signs, which are those of a tumor and not of a pneumonia.

From the tracheobronchial gland the tuberculous infiltration involves the gland surrounding the aorta and then extends to the mesenteric glands. The prevertebral glands become caseated and form a voluminous mass in front of the last dorsal vertebra, a second occurs in the ileocecal region, and a third surrounds the transverse colon. The clinical picture is that of a mildly progressive cachexia. The abdomen is distended, especially to the right, where, on careful palpation the enlarged glands can be made out. Rectal examination allows of a more accurate localization, and differentiates the glands from fecal masses. The child usually suffers from a diarrhea; the stools are soft and yellow and contain fat, the failure to absorb which explains the emaciation.

According to Combe's experience, generalization of the tuberculous process takes place most frequently by aspiration of tuberculous material into the bronchi. Depending on whether the tuberculous material empties itself into the bronchi or bronchioles, there occurs an acute caseous pneumonia or an acute caseous bronchopneumonia. The symptoms of acute caseous pneumonia resemble those of a frank pneumonia which has lasted a long period of time. In the early stages the diagnosis may be made from the following: Examination of the blood shows an eosinophilia during the entire course instead of after the crisis, as in the frank pneumonias. The Mantoux reaction remains positive, while in the frank pneumonias it disappears during the febrile stage. The Roentgen ray shows a dense irregular shadow, not limited to the lobes, as it is in the frank pneumonias. Following the early or

pneumonic stage is the stage of softening. The seventh day passes without a crisis, the condition remains grave, the fever seems of septic type, and the dyspnea continues. After a period of six or eight weeks, with remissions and exacerbations of the symptoms, the cough takes on the character of a whooping cough, and during an attack of coughing the child vomits a large amount of pus containing tubercle bacilli. Following these attacks of coughing there is a change in the physical findings. Instead of the bronchial souffle, many coarse râles, sometimes amphoric in character, are heard, and in the roentgenogram the dark pneumonic areas are replaced by shadows of cavities.

Caseous bronchopneumonia is one of the rarest forms of tuberculosis of infants. The tuberculous process starts at the hilus and gradually invades the lung, sometimes causing caseous infiltration of the periglandular tissue, sometimes forming numerous areas of caseous bronchopneumonia by aspiration of drops of pus into the bronchioles. These areas of caseous bronchopneumonia soften and empty themselves into the bronchioles and leave small cavities, "bronchopneumonic cavities"; also the peribronchial glands break down, forming a second group of cavities, "glandular cavities." The clinical picture is that of an ordinary bronchopneumonia with a very prolonged course.

The hematogenous forms of tuberculosis are rather frequent in infants. A softened gland opens into a blood vessel and a large number of tubercle bacilli are thrown into the circulation. If the rupture is into the pulmonary artery, a pulmonary miliary tuberculosis results; if into the pulmonary vein, a generalized miliary tuberculosis. An infant affected with acute pulmonary miliary tuberculosis presents all the signs of a febrile capillary bronchitis. The child is seized more or less suddenly with a constant cough, which nothing can alleviate, and which is accompanied with intense dyspnea and cyanosis. Somnolence alternates with restlessness. Examination of the lungs shows no definite signs of localization, but both lungs are filled with all varieties of râles. If the infant is already known to have a tuberculosis, the diagnosis of miliary pulmonary tuberculosis is not difficult, but if the child is seen for the first time, diagnosis is very difficult, especially as the Mantoux reaction is negative. The Roentgen ray, however, is of great help and shows a shadow having the appearance of granite or marble pathognomonic of miliary pulmonary tuberculosis.

Generalized miliary tuberculosis may be acute or subacute. In the acute form prodromal symptoms are exceptional, but, when they exist, they last weeks. These are anorexia, emaciation, cough, a change in disposition, and fever. The onset is sometimes sudden, marked by the appearance of fever, often accompanied by vomiting and diarrhea. Sometimes the onset resembles that of influenza (grippe) or the period of invasion of measles. General symptoms often entirely mask local

symptoms and the clinical picture is that of typhoid. On the part of the respiratory system the symptoms are the same as those of a pulmonary miliary tuberculosis, and the Roentgen ray shows the same findings. The abdominal symptoms are anorexia, vomiting and diarrhea. The abdomen is distended, in spite of the cerebral involvement, which is an important evidence of miliary tuberculosis of the peritoneum. Symptoms on the part of the nervous system are pronounced. The child is at first cross and irritable, then somnolent; the fontanel is distended; there is hyperesthesia and finally rigidity and convulsions. Ptosis, inequality of pupils, strabismus, and conjugate deviation of the eyes and head are usually found. Examination of the urine usually shows albumin.

Subacute generalized tuberculosis is an attenuated form. At first the symptoms are those of a gastric fever, but after several months, cough and prostration appear and finally all symptoms of an acute miliary tuberculosis. Necropsy shows, besides the tubercles of recent date, older tubercles in nearly all the organs, and these cause the symptoms falsely attributed to gastritis.

Under the terms localized miliary tuberculosis, Combe describes the so-called surgical forms of tuberculosis. There are usually metastatic lesions from a tuberculous endarteritis, occurring in connection with tuberculosis of the tracheobronchial glands. The osseous form is relatively frequent in infancy and occurs as an osteomyelitis, affecting usually the phalanges (spina ventosa), or as tuberculous caries of the short bones, affecting usually the vertebrae, more rarely as tuberculous gumma of the flat bones of the skull. Tuberculous arthritis, osteoarthritis, and synovitis are more frequent in young children than in infants, although they do occur at this age. Cutaneous tuberculosis is a frequent metastatic occurrence. The lesions are usually the papulosquamous, the papulonecrotic, or more rarely the gummous tuberculids, the so-called scrofulodermata of the German writers.

After the study of 133 cases, H. Koch[9] gives a description of tuberculosis in infancy. He recognizes five forms, according to the portal of entry: the bronchogenous, the placentogenous, the enterogenous, the stomatogenous, and the dermotogenous.

Of the first, the bronchogenous, Koch has gleaned some very decisive facts from the history of his cases as to the source of infection, for in fifty he definitely determined this. In twenty it was the father, in twenty-seven the mother, in one both parents, in one the grandparent, in one a brother, and in one a nurse. Less definite was the information regarding the time of infection, but in most instances it was surmised to be very early. In Koch's experience the infected infants lived from three to twelve months, regardless whether the baby was breast or artificially fed. Infants infected from the mother, how-

ever, succumbed earlier than those infected from the father, for the reason, Koch thinks, that the infection from the mother through more intimate contact occurred at an earlier period.

Koch agrees with Kuesz, Albrecht and Ghon, that the primary infection takes place in the lungs and then spreads through the lymphatics. He is not quite in accord with the division into stage of incubation, of primary, and of secondary lesion, and with the conception that tuberculosis, lues and other infections are identical. But, if this division is adhered to, he regards the incubation stage from the time of infection until the tuberculin test becomes positive. The stage of primary lesion is that of the development of the lesion at the point of infection. This stage ends when the process spreads to the regional lymph glands.

Knowledge of the primary lesion is based on necropsy findings. It is impossible for the clinician, because of its inaccessible position, to make a diagnosis of a primary lesion. Its presence can be suspected by a positive tuberculin test, and sometimes it can be seen in Roentgen-ray plates. The material used by the author in the study of the primary lesion is the same as described by Ghon in his monograph on "The Primary Pulmonary Lesion." In fifty-eight necropsy records, thirty-eight cases showed one primary lesion, eight showed two lesions, four three lesions, and one case four lesions. In the other eight cases widespread tuberculous changes involved the entire lobe in which the lesion occurred. The primary lesion varied in size from a pea to a child's fist, and was either a caseous nodule or a cavity. In only three cases was there any sign of healing. The right lower lobe was the most frequent location. It was either deep in the pulmonary tissue or subpleural. In the neighborhood of the subpleural lesion was frequently a pleuritic exudate.

Koch found the usual duration of the stage of incubation was six or seven weeks. Fever did not develop until late in this stage. There was no change in nutrition or in the blood picture. During the stage of primary lesion the temperature is periodically subnormal and never goes above 38 C. The chief symptom is the cough, and this occurred in seventeen of the thirty-five cases. In five cases there was pallor of the skin and mucous membranes and a normal blood picture. In three cases there was sweating.

Extension of the process in the lungs can take place by further development of the primary lesion. Sometimes the primary lesion is surrounded by tubercles, sometimes cavities form, and sometimes the entire lobe is transformed into a cheesy mass. There also occur isolated tuberculous lesions due to aspiration of material containing tubercle bacilli. These usually have the characteristics of a lobular pneumonia. Physical examination and the Roentgen ray are of con-

siderable help in diagnosing this stage. Cough is the most important symptom. Any type of temperature may occur.

From the primary lesions the tuberculous process spreads to the regional lymphatic glands. They caseate and soften and may rupture into the trachea or into a bronchus. Healing is rare in infancy. The chief symptoms of this stage are the harsh cough and expiratory stridor.

Extension to the upper respiratory tract may take place from the infected sputum, and in Koch's series there was one case of laryngeal tuberculosis and nine of pharyngeal and tonsillar tuberculosis. Extension to the intestinal tract may be caused by the infant swallowing the sputum. This occurred in forty-seven, or 35 per cent. of the writer's cases. In thirty-eight cases there were ulcers in the small and large intestines, in three a tuberculous peritonitis, and in six a tuberculosis of the mesenteric glands. Only exceptionally did the tuberculous ulcers cause symptoms, but the peritonitis caused abdominal tenderness, meteorism and diarrhea.

Extension also takes place through the circulation system. In the writer's series this form of extension caused osseous tuberculosis in five cases, tuberculosis of the skin in forty-four cases, usually of the papulosquamous variety, tuberculosis of the testicle in two cases, a solitary tubercle of the brain in one case and of the kidney in one case. If a richly infected material gains access to the circulation, a miliary tuberculosis, usually ending in tuberculous meningitis, results. The clinical picture depends on the localization of the miliary tubercles. The onset of miliary tuberculosis is only occasionally recognized. The condition is always accompanied by fever, usually continuous, but at times intermittent or remittent in type; only exceptionally is it subnormal. Emaciation is characteristic and sometimes there is severe anemia. If there are many tubercles in the lungs, dyspnea and cyanosis out of proportion to the physical findings occur. Often there is edema of the face and extremities and enlargement of the liver and spleen. An unfavorable sign is the appearance of tuberculids. The duration in the author's cases was from three to six weeks. Tuberculous meningitis has usually a sudden onset with fever. The infant loses appetite and is somnolent. Then symptoms of brain irritation, as vomiting, convulsions, and headache, develop. During the course of the disease there is stiffness of the neck, Kernig's sign, and dermographia. The sensorium becomes cloudy, and motor disturbances, like paralysis, especially in the region of the facial nerve, develop. The tendon reflexes are increased, the abdomen is sunken. The course is rapid, never longer than three or four weeks.

As to the outcome of tuberculosis in infants, Koch says that although most infants less than a year old die of miliary tuberculosis,

he agrees with other recent writers that the prognosis is not so hopeless as was once thought. The prognosis depends on the time and the severity of the infection.

Diagnosis is based on the cutaneous tuberculin test. A positive reaction not only shows infection but tuberculous disease, for it is known that every tuberculous process in infancy is active. Clinically, the diagnosis is based on the general and local symptoms already described. The Roentgen ray is important for diagnosis of tuberculosis in the chest.

Koch is not much in favor of the tuberculin treatment of tuberculosis in infants. He advocates breast feeding and careful nursing. Surgical measures are rarely considered, as osseous tuberculosis is not frequent. As a prophylactic measure, the importance of keeping infants away from sufferers from phthisis is emphasized.

After dealing so exhaustively with the bronchogenous form of tuberculosis, Koch discusses the rarer forms. He says infection through the placenta is possible and cites twenty authentic cases collected by Cornet. Infection occurs by passage of bacilli from the placenta into the fetal blood or by aspiration of infected amniotic fluid, this latter being really an instance of bronchogenous infection. Symptoms of placental tuberculosis are few. The infants are below weight at birth and do not thrive well. The temperature is irregular. In some cases there is marked pallor. There may occur tuberculids, multiple caries, or lesions in the lungs. Involvement of the abdominal organs, enlargement of the liver and spleen stand in the foreground of the picture. The diagnosis is based on the history, the marked involvement of the abdominal organs, the absence of symptoms on the part of the lungs, and the appearance of a positive tuberculin reaction in the sixth or seventh week of life.

Primary enterogenous and stomatogenous tuberculosis are very rare. In the author's series there were only four of the former and three of the latter. In two cases of the stomatogenous form the primary lesion was in the tonsil. Infection through the skin takes place only when there is an injury. The most frequent reported cases are those following circumcision.

H. Wessler and M. H. Bass[10] describe a form of tuberculosis in children which they call recurrent hilus infiltration. They believe that this form of tuberculosis is an extension from the lymph nodes and occurs frequently enough to warrant its incorporation as a clinical entity in the great group of tuberculous infections of the lungs. For a knowledge of its morphology, they say, we are indebted entirely to the Roentgen ray. The lesion occurs in the majority of cases on the right side, and its point of predilection is the lung in the immediate vicinity of the fissure between the upper and middle lobes. Beginning with its

base at the hilus, where a dark shadow of tuberculous nodes is present, a fairly opaque shadow of homogeneous density extends outward into the lung for a considerable distance, gradually fading into the normal lung tissue. The resulting infiltration is triangular in shape, its apex near the axilla. Its lower margin is sharply limited by the interlobular fissure. The latter is evidently thickened and is the seat of pleurisy, as it can usually be seen extending quite to the axilla beyond the limits of the infiltrated area. The infiltration does not remain constant in size or appearance, and this is perhaps the most remarkable fact in regard to these cases. The Roentgen-ray examination made at intervals of a month may show at first a wide area of infiltration, and at a later examination, nothing may be left but the thickened interlobular fissure. Such a sequence of infiltration and normal lung may be repeated several times and justifies the appellation of "recurring hilus tuberculosis."

The authors have found that children in whom this typical hilus involvement has occurred are usually brought to the physician on account of general debility, loss of weight, slight cough, or night sweats. Physical examination of the chest is often negative, unless the process has involved a considerable mass of lung tissue. This is a point of the greatest importance, for it emphasizes the fact that in debilitated children, with a positive von Pirquet test, Roentgen-ray examination is imperative. When the lesion is extensive, slight dulness to the right of the sternum may be present and expiration may be prolonged, harsh and accompanied by a few fine râles. The clinical picture is, moreover, peculiar, in that it shows considerable variation in the same case at different times. There is apparently a recurrent inflammatory process, which, as it extends from the hilus into the lungs, produces an exacerbation of the clinical signs and symptoms. At such times there is more rapid emaciation, more weakness, more fever, and possibly more cough. It is during such exacerbations that the Roentgen ray reveals the extension into the lung as described above. In the favorable cases, and the majority seem to be of this type, there is a distinct regression, the symptoms all becoming milder and the Roentgen ray coincidently showing a diminution in the amount of lung involvement.

E. Aine[11] describes ulcerative pulmonary tuberculosis in infants. He says that it was not exceptional to encounter in autopsies on infants who had died of tuberculosis, more or less extensive ulcerative lesions, analogous to those which characterize pulmonary tuberculosis in the adult. Anatomically, these ulcerative lesions occur in four forms. In the simplest form there is a single tuberculous cavity, which apparently represents the primary focus of infection, and is most frequent in infants from 3 to 6 months old. The second and most common

form consists of a cavity embedded in an area of caseous pneumonia. The cavity is large and multilocular, evidently the confluence of a number of smaller cavities primarily separated. The third form consists of small multiple cavities scattered through one lobe or one lung; they are always located around a bronchus and are due to breaking down of a caseous bronchopneumonia. In the fourth form the cavities are situated in the midst of dense fibrous tissue containing dilated bronchi. The author has observed that in all forms of ulcerative tuberculosis in infants the cavities are situated nearer the surface of the lung than in adults.

Cavity formation in infants gives rise to few clinical signs or symptoms, of which persistent dulness at the apex is most important; hemoptysis is of especial importance, but rarely occurs. Roentgenography is of great service in diagnosis.

W. P. Northrup[12] reports a case of disseminated miliary tuberculosis in a 15-months-old baby in whom the Roentgen ray proved a helpful diagnostic aid. The mother and one brother also had tuberculosis. The baby had been sick with wasting for one month before entering the hospital. Physical examination showed a poorly nourished infant, with discharging nose and enlarged glands. There was a papulopustular, umbilicated skin eruption, most abundant on the trunk, with a few lesions on the face and on the dorsal surface of the forearm. There was a pea-sized nodule in the subcutaneous tissue on the left forearm, one on the arm, one on each calf, symmetrically placed. One of these, removed and examined, proved to be tuberculous.

The physical signs in the chest were difficult to diagnose. The percussion note was unchanged, there was no bronchial voice or breathing, and no râles in front. At the angle of the scapula there were increased voice sounds and whistling râles. In a marantic infant these would not be conclusive, but the Roentgen ray helped to a diagnosis and showed a disseminated miliary tuberculosis of the lungs. In the absence of convincing chest finding and typical clinical tuberculous skin lesions, the Roentgen ray served here a most useful purpose.

J. Moore[13] reports a case of generalized tuberculosis with paralysis of the left oculomotor nerve which occurred after an attack of measles. The child had been well until the attack of measles a few weeks previously, and after that had bronchopneumonia. When she was admitted to the hospital the temperature was subnormal, and there was complete paralysis of the third nerve on the left side with dilatation of the pupil and inability to turn the eye inward and upward. There was also external strabismus and loss of power of accommodation and contraction to light. Ophthalmoscopic examination showed a choroiditis. The base of one lung was congested and the child had a cough.

On the basis of the subnormal temperature the author made a

diagnosis of tuberculosis, which was substantiated by the future course of the disease. Objective evidence of lung trouble increased and the child's strength failed rapidly. She became at first listless, then semi-comatose, and finally entirely unconscious. The abdomen had the scaphoid form so characteristic of tuberculous meningitis. Death occurred ten days after entrance.

Postmortem, there was found a disseminated tuberculosis of both lungs and of the mediastinal and peribronchial glands, pericardium, diaphragm, liver, kidneys, spleen, peritoneum, and of the basal meninges. No involvement could be made out of the nucleus or of the intracranial course of the third nerve either macroscopically or after hardening and examining sections.

J. L. Morse[14] has undertaken a study of D'Espine's sign, because of the difference of opinion which prevails as to what constitutes this sign, and because of his impression that it is much less frequent in the children of the well-to-do than in those of the hospital class, and, when present in the children of the well-to-do, it is in a considerable proportion of the cases not a manifestation of tuberculous infection. Six hundred and sixty-six patients seen in office and consultation practice form the basis of the study.

Both the whispered voice and the spoken voice were used in making the tests. In 626 of the 666 children, or 94 per cent., the change in voice sounds occurred between the seventh cervical and the first dorsal spine. These figures seem sufficient to prove that D'Espine's original contention as to the location of the normal change is correct.

The fact that this sign was present in but forty of 666 children, or only 6 per cent., shows that it is uncommon in the children of the better classes.

In eighteen, or nearly 50 per cent., of the children the enlargement causing D'Espine's sign was probably not tuberculous. In nine it probably was tuberculous, and in thirteen there were no data pointing one way or the other. These figures show what is now generally accepted, namely, that D'Espine was wrong in his conception that his sign was always a manifestation of tuberculosis of the bronchial glands. The presence of this sign means merely that there is some tissue between the trachea and bronchi and vertebral column which transmits the bronchial sound unchanged, whereas under normal conditions it is modified during transmission.

M. S. Reuben[15] discusses fever as the initial sign of tuberculous infection in children. He bases his conclusions on the study of infants coming to the milk station. In three instances the exact time of onset of the tuberculous infection was determined, as the children were under observation from early infancy. In each of these the mother was tuberculous. The cutaneous tuberculin reaction was performed on

these infants once every month and found negative as long as the infant was gaining in weight and had no fever; with the onset of fever, however, a positive reaction was obtained in two of these cases, and in the third a positive reaction after the fever had lasted a week.

Reuben believes that fever is the first sign of tuberculous infection in infants. The fever is of sudden onset; at first is high and remittent in character, then gradually falls by lysis, but not to normal; it continues slightly above normal, 100 to 101 F. for twelve to twenty weeks, with periods of complete absence of fever. Exacerbations of high fever, of the same type as that of the onset, usually occur. The tuberculin reaction in these cases becomes positive at the onset of fever or within a few days. At first there are no physical signs, but these develop within the course of a few weeks. In patients who recover they gradually disappear. The prognosis of tuberculous infection in infancy is more favorable than was formerly supposed; 30 to 35 per cent. survive the infection.

Reuben also found that in infants 14 per cent. of prolonged febrile conditions diagnosed as influenza gave a positive von Pirquet reaction, and he thinks it possible that many other fevers of obscure origin may be due to tuberculous infection. He urges that a tuberculin test should be carried out on every infant who has an idiopathic fever and presents no physical signs.

H. Kleinschmidt[16] believes that the assumption of an initial fever in tuberculosis must be deferred until more data on the subject have been accumulated. He reports a case of an infant nursed by the mother who was suffering from tuberculosis in an advanced form and who died shortly after the child's birth. The child seemed to thrive on a simple milk mixture and had a temperature constantly normal. On the fifty-first day the von Pirquet test became positive and it was not until two weeks later that the child developed fever. Symptoms of generalized tuberculosis rapidly followed and the child died at the age of 3 months.

According to L. Jeanneret,[18] the frequency of digestive disturbances in the tuberculous child has long attracted the attention of pediatricians. He divides these disturbances into primary and secondary dyspepsias. The secondary form is due to overfeeding, and Combe was the first to draw attention to the numerous cases of enteritis due to superalimentation. Secondary dyspepsias are more frequent in private practice, where parents still have the false idea of the necessity of overfeeding and of giving much medicine. In the hospitals, where the régime is simple, this form is never observed.

Jeanneret has carefully gone over the histories of his tuberculous children and has found that 50 per cent. suffered from primary dyspepsia. Very often this digestive disturbance was the first symptom

and led the parents to consult the physician. Primary dyspepsias in tuberculous children may be mild or severe. In some instances the patients present the picture of a chronic enteritis and always are seriously handicapped.

The author's treatment is as follows: As he found in thirty-five of 120 of his cases an anachlorhydria, he gives an amount of food proportionate to the quality of the digestive juice, which is ascertained by gastric analysis. He diminishes the kind of food which requires acid for digestion, but does not suppress meat entirely, since it is an excitant of gastric secretion. To supply the deficient secretion he gives a teaspoonful of the following mixture after each meal: 3 parts pepsin; 5 parts hydrochloric acid; 50 parts syrup of raspberry and water to 120 parts. Under this régime the digestive disturbances quickly disappear.

A lack of uniformity in the blood picture of tuberculous meningitis observed at the Babies' Hospital has led E. A. Morgan[19] to attempt establishing an average figure for the blood count in this condition. For this purpose 169 cases of tuberculous meningitis from the records of the hospital for the last eight years were analyzed. There were 252 counts made on the 169 cases.

The conclusions drawn were as follows: The leukocyte count in tuberculous meningitis is higher than has heretofore been described. The average in this series was 20,900 per c.mm. with 72.6 per cent. polymorphonuclears. The total leukocyte count and the proportion of polymorphonuclear cells vary with the stage of the disease; that is, both counts increase as the disease advances. There is a relative but not absolute diminution in the mononuclear elements of the blood. There is a definite relationship between the intensity of the tuberculin reaction, on the one hand, and the total leukocyte count and polynuclear percentage, on the other. Diminution in the intensity of the tuberculin reaction is accompanied by an increase in the total leukocyte count and polymorphonuclear percentage, both being evidence of a failing resistance of the body to the tuberculous infection.

L. Morquio[20] reports six cases of tuberculous meningitis in which the spinal fluid showed a polymorphonuclear leukocytosis. The first case was a 14-year-old girl who entered the hospital Sept. 14, 1910, with symptoms of meningitis. Lumbar puncture on the 24th gave a clear fluid with 310 cells to the c.mm., 53 per cent. of which were polymorphonuclears and 47 per cent. lymphocytes. On the 27th another puncture gave a slightly cloudy fluid, containing 780 cells to the c.mm., 47 per cent. of which were polymorphonuclears and 53 per cent. lymphocytes. The second case was an 11-year-old girl. In the spinal fluid were 50 per cent. polymorphonuclear cells and 50 per cent. lymphocytes. In the third case, a 6-year-old boy, the spinal fluid was slightly

cloudy and showed 98 per cent. polymorphonuclear cells. In the fourth case, also a 6-year-old boy, the spinal fluid contained 80 per cent. polymorphonuclears and 20 per cent. lymphocytes. In the fifth case there were 62 per cent. polymorphonuclears and 38 per cent. lymphocytes, and in the sixth, 75 per cent. polymorphonuclears and 25 per cent. lymphocytes.

Ferdinando[21] reports a case of tuberculous meningitis followed by recovery. The patient was an 11-year-old girl with a family history of tuberculosis. She had been sick fifteen days with cough and irregular fever. Examination on entrance to hospital showed pallor, emaciation, and micropolyadenopathy. There was convergent strabismus, ptosis of the right eyelid, stiffness of the neck, Kernig's sign, spasmodic muscular movements, hyperesthesia and rough breathing over the lungs posteriorly. Lumbar puncture gave 40 c.c. of clear fluid containing lymphocytes and tubercle bacilli. After puncture all symptoms subsided and in about fifteen days the child was considered cured.

G. Fiore[22] adds the report of another case of recovery from tuberculous meningitis to the two others which he has previously reported. The third patient was an 8-year-old girl who had had convulsions when 1 month old. She was admitted to the hospital with signs of lymphatism, tracheobronchial adenitis and bronchopneumonia. The von Pirquet test was strongly positive. The bronchopneumonia cleared up, leaving only a patch of harsh breathing at the apex of the right lung. Shortly afterwards there developed vomiting, headache, drowsiness, irregular fever, increased reflexes, dermographia and cranial tympany on percussion. Lumbar puncture gave abundant clear fluid under pressure, which contained an increased number of lymphocytes and amount of albumin, and which produced tuberculosis in a guinea-pig. The patient's condition remained unchanged for a month, then began to improve, so that at the end of six months, recovery was complete. Lumbar puncture was practiced eight times and each time the pressure was less and the lymphocytes and albumin diminished.

Jaquerod[23] believes that there is a causal relation between tuberculosis and erythema nodosum and that the association of the two is not merely a coincidence. He reports two cases of erythema nodosum, one in a girl of 10, the other in a boy of 5, extremely severe but with rapid and apparently complete recovery. Both children had latent glandular tuberculosis and the eruption appeared after an acute gastritis in the former and an attack of influenza in the latter. Jaquerod thinks these intercurrent affections aroused the tubercle bacilli and produced a transient tuberculous toxemia, which in turn was responsible for the erythema. The prognosis is that of the tuberculous infection, and there is no reason to believe that those who develop erythema nodosum are more likely than those who do not, to have serious tuberculosis later. The author has had a number of patients with erythema

nodosum who are now in robust health after periods ranging up to fifteen years.

H. W. Barber[24] reports a case of lichenoid and nodular tuberculid in a 4½-year-old boy. Following an attack of measles an eruption appeared, first on the hands and knees and then on the trunk. The lesions on the trunk were lichenoid and those on the hands and knees nodular. Physical examination of the chest revealed signs of enlarged bronchial glands.

Little[25] reports a case of lichen scrofulosorum in a 13-year-old girl who had been treated for two years with small doses of tuberculin in the form of bacillary emulsion, for scrofuloderma of the neck of five years' duration. Lichen scrofulosorum had recently appeared suddenly in the form of a large number of patches of grouped follicular papules, the patches forming oblong or circinate shapes, from 1 inch to 4 inches in diameter, and distributed on the front of the trunk, between the navel and the nipples, and on the back. The papules were of a vivid red, somewhat more salient and vivid in color at the periphery. The patches had persisted with little change except that there was a slow but progressive fading of color, due probably to the omission of the tuberculin injections.

The same writer[26] also reports a case of acute disseminated tuberculosis cutis in a male infant 7 months old, eruption having come out acutely about a fortnight before. The whole of the skin from the buttocks to the feet was closely covered with an eruption of small, deep bluish, nodular lesions, varying in size from 1/16 inch to ¼ inch. Above the level of the pubes the skin was unaffected. The cervical glands had become enlarged at the age of 2 months, and the mastoid had been operated on for tuberculous disease at the age of 3 months. After the removal of about twelve caseous glands, in which bacilli were easily found, the eruption faded considerably.

D. McKenzie[27] has undertaken a study to determine whether any relation except accidental existed between ozena and tuberculosis. He has ascertained the following facts: Tuberculosis was found in the majority of necropsies on ozenatous patients. Clinical examination revealed tuberculosis in 20 to 58 per cent. A family history was revealed in 46 to 90 per cent. The von Pirquet test was positive in 80 per cent. of the patients under 15 years of age, and the subcutaneous test in 94 per cent. From these observations McKenzie draws the following conclusions. There is evidence of the frequent association of tuberculosis and ozena, in the clinical examination, the family history, and in the result of the tuberculin tests. This evidence is supported by the results of tuberculin treatment. There is also evidence that the acid fast bacillus in the ozenatous crusts in an attenuated form of tubercle bacillus. Ozena in many details resembles other paratuberculous diseases.

DIAGNOSIS

28. Combe: Diagnosis of Tuberculosis in Infancy, Le Nourrisson, 1916, **4,** 1.
29. Smith, C. J., and Bibby, H. L.: Observations on Tuberculosis at the Vanderbilt Clinic, Arch. Pediat., 1916, **33,** 782.
30. Dunn, C. H.: Tuberculosis in Infancy, Am. Jour. Dis. Child., 1916, **11,** 85.
31. Sedgwick, J. P.: Diagnosis of Early Tuberculosis in Childhood, St. Paul Med. Jour., 1916, **18,** 213.
32. Zitronblatt, A. Y.: Skin Tuberculin Test in Surgical Tuberculosis, Russk. Vrach., 1915, **14,** 708.

Combe[28] bases the diagnosis of tuberculosis in infants on the following: 1, heredity; 2, the general appearance; 3, the Roentgen-ray examination; 4, bacteriologic tests; 5, tuberculin tests; 6, the clinical examination.

The author's statistics show a family history of tuberculosis in 90 per cent. of his cases, if in the word family is included all who live in intimate contact with the family. A careful detailed history is of great value in diagnosis, but must include not only father and mother, but brothers, sisters, servants; in fact, everyone closely associated with the child.

The appearance of the infant is most deceptive in regard to diagnosis of tuberculosis. On the one hand, a tuberculous infant may appear absolutely normal, while on the other, an infant with atrepsia or a chronic bronchopneumonia may be so cachectic that the diagnosis of tuberculosis seems certain. However, there exists a condition in the infant suffering from tuberculosis which Combe calls "facies vasodilatation," and which suggests at once further search for the disease. Infants with "facies dilatation" are cyanotic, they appear old for their age, they have long curly lashes, eyebrows and hair, bright eyes, overred lips, and a hairy, moist skin. In the presence of this condition Combe suggests search for tuberculous lesions in the bones of the skull, the phalanges, and joints. Papulonecrotic tuberculids may be discovered on the trunk, shoulders or limbs, chronic tuberculous ulcerations in the skin, or masses of glands in the subclavicular or submaxillary regions. Or there may be a phlyctenular keratitis or chronic suppurative otitis media, with multiple perforations of the drum and formation of granulations, so characteristic of tuberculosis of the middle ear.

Examination with the Roentgen ray shows enlargement of the bronchial glands or areas of consolidation in the lungs. It does not, however, indicate whether the enlargement is the result of an influenza infection or a previous bronchopneumonia, or whether the pulmonary shadows are the remains of a fibrinous pneumonia or of an atelectasis. The radioscopic examination alone leads to an erroneous diagnosis. It must be interpreted and substantiated by clinical and biologic tests.

Bacteriologic examination allows of a positive diagnosis, but finding the tubercle bacillus is often difficult, as the sputum is usually swallowed. The author has, however, often been able to demonstrate tubercle bacilli in the vomitus or stomach washing or feces, or in the mucus obtained by swabbing out the pharynx.

Combe regards the Mantoux intradermal tuberculin reaction as more exact, more reliable and more sensitive than the von Pirquet test. For six years he has used the von Pirquet test on one arm and the Mantoux on the other and thus in many hundreds of infants has compared the value of the two tests. To perform the test, he injects into the skin of the arm $\frac{1}{10}$ mg. of old tuberculin. Combe describes four types of reactions. A normal reaction, in which in twenty-four hours there is the formation of a red papule of varying dimensions. The scrofulous reaction, in which the papule is more prominent and is surrounded by a painful area of redness 5 to 10 cm. in diameter. This reaction occurs in children with the exudative diathesis. In some instances the papule becomes capped with more or less numerous vesicles, which, on drying, leave a pigmentation. In other instances a pustule caps the papule, which, on healing, leaves a small scar. The value of this test depends on its proper performance and the correct interpretation of the reactions. The author believes that a positive reaction indicates that the infant has been infected with the tubercle bacillus, but does not indicate whether the resulting condition is a latent tuberculosis in evolution or a cured tuberculosis. A negative Mantoux reaction, on the other hand, does not exclude tuberculosis. In the first place, if the infection is recent, the infant may not have had time to produce sufficient antibodies to cause a reaction, and the test should be repeated every month for at least three months. In the second place, it is necessary that the organism be capable of forming antibodies. In profound cachexia and just before death this faculty is lost. In cases of miliary tuberculosis the antibodies are absorbed by the tuberculin already produced in the organism. A number of acute infections prevent the formation and cause the absorption of antibodies. A negative Mantoux reaction, then, is due to the absence of antibodies, not to the absence of a tuberculous infection.

The inspiratory and expiratory stridor, the harsh bitonal cough, and the spasmodic attacks of cough resembling whooping cough seem, according to the writer, to be most important symptoms. The inspiratory stridor, due to pressure of enlarged bronchial glands on the trachea, must be differentiated from the inspiratory stridor of laryngeal obstruction. In laryngeal stenosis the child throws its head backward, to open, as far as possible, the larynx; in tracheal stenosis the head is thrown forward. In laryngeal stenosis the voice is altered, while in tracheal stenosis it remains normal. In laryngeal stenosis the larynx

descends during inspiration, in tracheal it remains stationary. The bitonal cough is due to the lack of symmetrical functioning of the vocal cords, so that the sound emitted by each differs in pitch. The attacks of spasmodic cough are differentiated from those of whooping cough by the absence of the crow at the end of expiration, by the fact that the attacks do not occur regularly and are not more frequent at night. The expiratory stridor is the most important sign, because it occurs early and is not found in any other condition. Inspiration is silent, but expiration is noisy and prolonged.

C. H. Smith and H. L. Bibby[29] report their observations at the Vanderbilt Clinic on tuberculosis in children. When a child was brought for examination, they asked two questions: (1) Has the child been infected with tuberculosis? (This question was answered by the skin test.) (2) Is the infection latent or active? Active and latent seem terms preferable to infection and disease, since they are more accurate, and since all infection means disease. An active tuberculosis in a child was not like an incipient tuberculosis in an adult. The diagnosis in the child was made on symptoms of impaired nutrition and anemia, undersize, and failure to gain in weight. The presence of fever lasting over a considerable length of time was suggestive. Other valuable symptoms were anorexia, fatigue, languor, headache, and night sweats. In children, cough and positive chest signs were rare, but there might be transient bronchitis, asthmatic bronchitis, and enlarged bronchial glands. The authors found physical signs in the lungs in only twenty-one of 150 cases. The physical signs were transient, localized râles at the apex in one case, localized râles in the axilla in three cases, generalized bronchitis in two cases, asthmatic bronchitis in five cases, pleurisy in four cases, consolidation with cavity formation in four cases. The signs of involvement of the bronchial glands were dulness, tender spine, and D'Espine's sign.

The writer thinks that the Roentgen-ray is of value only when a short exposure can be made. Enlarged bronchial glands or tracheal-bronchial involvement might give large central shadows or small nodes might give shadows along the bronchi.

C. H. Dunn[30] found in a series of sixty-two successive necropsies on children in the first two years of life that tuberculosis was considered the direct cause of death in twenty-three cases and the contributing cause in two. He therefore emphasizes the importance of tuberculosis in infancy.

In this series of necropsies Dunn investigated the question of primary lesion, and as a result, it was actually found at the portal of entry in twenty-two of the twenty-five cases. He believes with Ghon that, when a primary lesion is not found at the portal of entry, it is overlooked. The fact that the primary lesion was found in the lung

in twenty cases and in the intestine in two cases suggests that in Boston at least the most frequent mode of infection is by inhalation of tubercle bacilli from a human source, but that infection through the ingestion of bovine bacilli in contaminated milk may occur.

The lesion found in the lung seemed quite easily recognizable as a primary lesion, and distinguishable from the widespread secondary lesions. In most cases it was a circular area, varying in size from that of a pea to that of a hazelnut. The center was caseous, but usually of a grayer color than the yellowish-white caseation seen in the secondary lesions. In some there was caseous softening or small cavities; in one there was calcification. In a few cases the primary lesion was much larger, reaching to the pleura, where its situation was marked by firm fibrous adhesions. Around the periphery of some of the smaller lesions were numerous miliary tubercles, suggesting direct extension. The favorite situations of the primary lesions were at the apex and near the hilus. The lesion found in the intestine and considered primary was a tuberculous ulceration.

The secondary lesions found in the lungs were of two distinct kinds. One was a tuberculous bronchopneumonia, characterized by exudate into the pulmonary alveoli, with more or less necrosis or caseation. The other secondary lesion was a miliary tuberculosis. The bovine type of bacillus was found in one case, and the human type in four.

A diagnosis of the tuberculous nature of the disease was made during life in twenty-three of the twenty-five cases, and was based on (1) the finding in the chest of physical signs which suggest tuberculosis; (2) the evidence given by the tuberculin test; (3) the evidence given by Roentgen-ray examination of the chest. Signs suggesting tuberculosis were found in fourteen of the twenty-five cases. In comparing the physical signs with the postmortem findings the following conclusions were drawn: 1. Acute miliary tuberculosis of the lung without tuberculous bronchopneumonia gives no recognizable signs in the lung. 2. Tuberculous bronchopneumonia usually does give signs; in some cases only scattered râles, in others signs of consolidation in various parts of the chest. 3. The presence of d'Espine's sign in infancy usually means tuberculosis of the bronchial lymph nodes, but the sign may possibly not be obtained, although the glands are found enlarged at necropsy. 4. The primary lesion gives no signs in the chest, unless very large, and in such cases the signs are only those of consolidation and are indistinguishable from tuberculous bronchopneumonia.

In testing the reaction to tuberculin only the von Pirquet test was employed. On the whole, the author is inclined to believe that the value of the cutaneous tuberculin reaction in infancy is not so great as many writers and statistical reports have inferred. A negative

reaction seems to be a frequent finding in any stage of the disease and gives no evidence at all. A positive reaction, on the other hand, means tuberculosis.

Roentgen-ray examination of the chest was made in thirteen cases, and was positive in every case. In several cases it was the only positive finding. In general, there was a surprisingly close correspondence between the Roentgen-ray picture and postmortem findings. The enlargement of the bronchial lymph nodes could be made out in most cases. Tuberculous bronchopneumonia was correctly diagnosed in several cases, but not in all in which it was found postmortem. The primary lesion was not shown, when small, but was conspicuous when very large. Miliary tuberculosis of the lung without tuberculous bronchopneumonia was not shown.

PROGNOSIS

33. Combe: Prognosis of Tuberculosis in Infants, Le Nourrisson, 1916, **4,** 202.

34. Permin, G. E.: The Skin Tuberculin Test in the Prognosis of Tuberculosis in Young Children, Hospitalstidende, 1916, **59,** 697.

According to Combe,[33] the opinions of pediatricians differ as to the prognosis of tuberculosis in infants. While most declare that, when diagnosed clinically it is absolutely fatal, others affirm that they have seen infants survive tuberculous disease. Combe is of the opinion that the prognosis of tuberculosis in infants is very grave, but not inevitably fatal. He thinks the outcome depends on a number of factors. The age of the child at the time of infection is the first point to consider. The younger the child is at this time, the less capable he is of defending himself and the greater is the tendency of the tuberculosis to become generalized. The virulence of infection and the opportunity for reinfection are important factors. Contact with open tuberculosis offers this opportunity for reinfection. It is usually admitted that infection from the mother is more dangerous than that from other members of the family, and that the danger is the result of reinfection.

The clinical form of the disease is most important in prognosis. If when the diagnosis is made the tuberculosis is still localized in the glands, a less serious prognosis can be given. If the glandular barrier is broken down and there is mediastinal and hilus infiltration, the case must be regarded as very serious, although the author affirms that he has seen symptoms recede and apparent recovery result from tuberculin therapy. If signs of generalized tuberculosis are present and the Roentgen ray confirms the diagnosis of miliary tuberculosis or of acute caseous pneumonia, the case must be regarded as desperate. Chronic surgical tuberculosis is the only form which offers a good prognosis and is caused by a spontaneous autotuberculin therapy from the slow progressive penetration of tuberculin into the general circulation.

The behavior of the tuberculin reaction is the last factor to be considered in prognosis of tuberculosis of infants, and Combe thinks that valuable data regarding prognosis can be obtained from a series of Mantoux intradermal tests. The test is given every fifteen days with the same amount of tuberculin, and, if in these circumstances, the reaction each time becomes more marked, it must be inferred that there is an increasing amount of tuberculin secreted and that the lesion is becoming more aggravated. Combe calls this the Mantoux anaphylactic reaction. If, on the other hand, the intensity of the reaction diminishes in intensity each time, until it disappears, either the lesion is secreting less tuberculin or the organism is producing more antibodies which unite with the tuberculin. This reaction Combe calls Mantoux immunity and regards as of favorable import.

Combe considers still another question, namely, the duration of tuberculous disease in infants. He says that, so long as the disease is limited to the glands, it spreads slowly, may last months, and may even be cured. In case of spread through the blood vessels with a resulting miliary tuberculosis, the course is of only a few weeks' duration. In the case of a caseous pneumonia the duration is a few months. In tabes mesentericus and hilus tabes, death takes place from a progressive cachexia and the disease lasts two or even three years.

G. E. Permin[34] has studied the skin tuberculin test in regard to the prognosis of tuberculosis in infancy and concludes that only during the first year of life does a positive reaction indicate a grave outcome. His conclusions are based on tests performed on the children of patients who apply to the two antituberculosis dispensaries in Copenhagen. In all, forty-six tests were made. Of fifteen infants less than a year old, six died, but only two of thirty-one between 1 and 2 years. Many of the children who had been repeatedly exposed to infection seemed to thrive through quite a long period of observation.

PROPHYLAXIS

35. Knopf, S. A.: The Period of Life at which Infection from Tuberculosis Occurs most Frequently, Med. Rec., New York, 1916, **84,** 47.

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S. A. Knopf[35] discusses the period of life at which infections from tuberculosis occur most frequently and how their frequency can be diminished and prevented from becoming tuberculous disease. He bases his conclusions not only on his own experience, but on the answers to forty letters to well-known specialists on tuberculosis and internists, and on twenty letters to well-known authorities on diseases of children. He adds to the results of this correspondence whatever important enlightenment he could find by perusal of the recent literature.

Summarizing the results of this study, Knopf says that the age at which a tuberculous infection contracted in infancy or childhood becomes active was, according to the majority of correspondents, at, or shortly after, 15 years; next, between 18 and 30 years. Nearly all of the authorities consulted unite in the opinion that, in order to combat tuberculosis successfully in the young and old, the sources of infection in childhood must be diminished, and Knopf enumerates the measures which he hopes may tend to diminish this frequency of infection, and, when it does occur, prevent the disease from developing. He says we must seek to amend the federal and state laws which make it a criminal offense for a duly licensed physician in good standing to give advice concerning the means of preventing conception. All cases of open tuberculosis should be required by law to be reported to the health authorities, who in turn should be authorized to send the patient instructions to prevent infecting others. Cases which cannot be properly taken care of in the home, or when it is evident that they constitute centers of infection, should be transferred to sanatoriums, special hospitals, or at least to special wards in general hospitals.

For the pregnant tuberculous woman there should be a maternity sanatorium or a special ward in existing maternities, where prolonged antituberculous treatment can be effectually carried out, and where mothers can receive such instructions as will guard their offspring from postnatal infection. Where there is the slightest suspicion of tuberculous infection the child should have a healthy wetnurse or should be

bottle fed. Enterprises for the purpose of providing medically supervised country homes for tuberculous mothers and their children should be helped by private philanthropy or by the aid of the municipality. All children under 5 years of age should be subjected annually, or even semiannually, to the von Pirquet test, and all who react positively and have symptoms and physical signs in addition should be placed under proper treatment. All children between 5 and 15 years of age, particularly those attending public schools, should be subjected to a careful physical examination on entering, and an annual reexamination thereafter, always accompanied by a von Pirquet test. Those reacting positively and showing physical signs, those evidently predisposed to tuberculosis, should be placed in open air classes, open air schools, preventoriums, seaside or inland sanatoriums. Open air instruction should be practiced, whenever feasible. Calisthenics, breathing exercises and swimming lessons should constitute a part of the curriculum of every public and private school. The school authorities should have the right to investigate the home of any child attending public school, when the teacher or school physician thinks that underfeeding, bad sanitary home environments, or child labor at home are responsible for a poor physical condition, which might develop into tuberculosis.

Child labor must be done away with. There should be an obligatory examination for tuberculosis and other serious diseases of every boy or girl prior to entering college or any occupation. There should be periodical examinations for tuberculosis of all employees. For those weeded out as tuberculous or afflicted with other diseases, there should be agricultural and industrial colonies. There also the graduates from sanatoriums should be sent for an opportunity to regain strength and vigor, to make their cure more lasting, and above all to learn again to earn their living. There should be state insurance or obligatory private insurance against accident, old age, and diseases, including tuberculosis, for all earning less than $1,000 per annum. Uniform bovine laws should be enforced by federal authorities in all states of the Union alike. With all this there must be continued propaganda for the education of the masses concerning the prevention of tuberculosis, alcoholism and other social diseases; for the improvement of housing conditions; for the prevention of injurious overwork; for healthful recreation of the masses in city and country; for the return to the soil from our overcrowded cities; and above all, for a living wage for all who labor honestly and efficiently, and a rational and speedy solution of the problem of unemployment.

The measures outlined will prevent a benign infection from becoming disease and render the young child or adolescent less likely to future infection by increasing the natural resistance. The most expedient way to carry out the suggested program would be by a

federal commission on tuberculosis, as has been suggested by the writer a number of times.

S. C. Kingsley[36] outlines a program for the promotion of the physical welfare of children and the prevention of tuberculosis among them, which was drawn up by the committee appointed at the meeting of the Mississippi Valley Tuberculosis Conference.

The work was divided into two classes: 1. The creation and promotion of institutions and agencies for the care and relief of those who are the victims of the disease and for safeguarding their families and associates. 2. The conduct of a vigorous department of education and propaganda.

Under the first heading come: (a) careful medical examination of patients, and, through children's clinics, of children in families of tuberculous persons; (b) sufficient and efficient hospital provisions for advanced cases by municipalities and counties; (c) sanatoriums for incipient cases, with adequate provisions for children; (d) open air schools; (e) sanatorium extension work, equipment of porches, roofs, etc., and special home relief, including cooperation with city and county relief agencies and charities of the community; (f) medical examination of employees and inspection for promoting shop sanitation and wholesome working conditions; (g) Christmas seal campaign; (h) infant welfare movements.

The second division of work is the department of education and propaganda. Most effectual work can be done by arming and setting to work already organized forces in the community, of which the following are common: 1. the public school with its teachers and officers; 2. state and local boards of health; 3. board of county commissioners; 4. city or county medical societies; 5. the country editor; 6. granges and farmers' alliances; 7. labor unions and fraternal orders; 8. women's clubs; 9. church organizations.

All these agencies afford opportunities for the most vital cooperation. Definite study should be given to the plan of approach and to the preparation of material for the different groups.

L. Jeanneret[37] believes that the school should take the lead in the fight against tuberculosis. Three forms of tuberculosis are of especial interest to the school physician. In the first the bacilli are quiescent in the glands and do not reveal their presence by physical signs, except a positive reaction to tuberculin. The second form Jeanneret calls tuberculosis in evolution. From time to time the bacilli in the glands take on activity and produce signs of intoxication in the child. The physical development is retarded and the hypoplastic type of Hutinel is presented. In the third group are the active forms. Among 123 tuberculous children between 5 and 15 years of age the author found sixty tuberculinized, thirty-two with tuberculous glands, seven with active

tuberculosis, eighteen with latent pulmonary tuberculosis, and six with other forms. Because of the small number of active cases there is little danger of the child acquiring the infection in the school.

Jeanneret considers the method by which the school authorities can most easily detect the disease. He says that every child should have a health chart on which should be recorded his weight once a month, and his height twice a year. The weight divided by the height gives a reliable index of the physiologic balance. The chart should record also the color of the skin and mucous membranes, any anomalies noticed, and the result of the von Pirquet test. The von Pirquet test is indispensable. Once positive, it need not be repeated, but if negative, it should be repeated every year. Jeanneret thinks a Roentgen-ray machine a valuable adjunct to the school's equipment. He calls attention also to the importance of excluding tuberculous teachers from the schools, insisting on a rigid examination for all candidates.

As soon as a child with tuberculosis is discovered in school, he should be placed in a proper institution. Beside the removal of active cases, Jeanneret mentions a number of other measures which protect the schoolchild. Hygiene of the schoolbuilding is important, pure air in the schoolroom, and proper methods of sweeping and cleaning. Lessons in personal hygiene also are important. Periods of stress should be guarded against. Between the years of 5 and 9 the school program should be simple, and periods of recreation frequent. Jeanneret regards sunshine as the surest preventive of tuberculosis, and advocates gymnastics and exercises in the open air with the upper part of the body exposed. For children between 6 and 12 years these exercises should be predominately thoracic.

Weith[38] does not agree with Jeanneret as to the value of the von Pirquet test in schoolchildren, or that it should be obligatory in all schools. In the first place he thinks that the test is not entirely devoid of danger, and quotes a number of reports of children with scrofulous affections suffering violent exacerbations of the skin affection after a von Pirquet test. He found also instances of phlyctenular conjunctivitis and of general disturbance after the test. Nor does he think the test infallible. He has found in the literature reports of cases in which necropsy showed no tuberculous lesion when there was a positive von Pirquet test during life, and, on the other hand, necropsy has sometimes shown tuberculous lesions, when the test was negative. He believes the von Pirquet is not absolutely necessary for the diagnosis of tuberculosis and quotes Jeanneret himself as saying that most children who give a positive reaction are frail, delicate, anemic and suffer from scrofula and general adenopathy. Weith believes that other means are much more important in diminishing tuberculosis among schoolchildren, improving hygiene in the home, propaganda against alcohol, etc.

W. C. Gwynn[39] emphasizes the fact that the protection of the child from infection with the tubercle bacillus can be obtained only by the exclusion from the public school of the open case of phthisis, in teacher and pupil. Any system of school inspection to be thorough must include the teacher, because of her close association with the pupils. Exclusion of pupil does not offer great difficulty, as tubercle bacilli are rarely found in the sputum of children and, when they are, the children are too sick to be benefited by attendance at school. Children with closed tuberculosis, which is the common type, should be segregated in open air schools, not only because this is the ideal method of treatment, but because it is never known when a closed case will become open and do incalculable harm before detection.

H. W. Dana,[40] from wide study among schoolchildren, concludes that the period for infection is frequently childhood, and that from this early infection follows most of the active tuberculosis of later life. He thinks the general practioner has not been interested in the diagnosis of tuberculous infection in children and has not awakened to its practical importance. In fact, the general practitioner tends to deny the existence of tuberculous infection in children.

According to Dana, it is a safe general rule to follow, that any child who shows constantly poor nutrition, fever, lack of vitality and ambition and abnormal pallor should have the benefit of fresh air, abundant and suitable food, as well as frequent, careful physical examination by an expert. Children suffering from tuberculous infection should be sought for by the school physician, and, when found, should be taken by the school or district nurse at stated intervals to the local tuberculosis dispensary for examination. Dana does not place much value on the Roentgen ray in distinguishing between cases needing active treatment and latent or healed cases.

L. Jeanneret[41] lays stress on the great importance of removing the new-born child from the home when there is a case of open tuberculosis. This is done as a prophylactic measure against tuberculous meningitis and miliary tuberculosis, forms of tuberculosis which are second only to gastro-intestinal diseases in mortality statistics of infancy. As soon as the child has passed its eighteenth or nineteenth month, when the greatest danger of generalization of the tuberculous infection is past, it can be restored to its parents, but even at this time advice in regard to prevention of infection must be given.

Jeanneret thinks the ideal way for taking care of infants of tuberculous parents is to organize institutions where the infant can be taken at birth and where the parents can visit the child and watch its progress without coming in direct contact with it.

In case the infant has already become infected, the author puts his faith in intradermal injections of tuberculin as a prophylactic measure

against generalization of the infection. This method creates in the skin a focus from which tuberculin is gradually absorbed into the general circulation and stimulates the production of specific antibodies. The artificial focus is maintained by repeated injections.

Intradermal injections are simple and easy. The skin is pinched up into a fold and the very fine needle is introduced, parallel to the surface. Jeanneret injects 0.01 c.c. of a 1 : 1,000 solution, repeating the injection every third day and increasing the strength very gradually, till 0.1 c.c. of a 1 : 10 solution is reached. The local reaction is less in infants than in older children. As the child grows older it manufactures its own tuberculin in its tuberculous glands and does not need artificial tuberculinization. Jeanneret is confident that he has saved certain infants by these prompt measures and does not hesitate to recommend them even when the prognosis is grave.

Y. Ustvedt[42] has compiled infant mortality statistics in tuberculous families. He thinks that unquestionably valuable lessons can be deduced from such figures. His material includes 480 infants born in families with one or more members suffering from tuberculosis in the contagious stage. An average of 19.2 per cent. of these infants died during the first year of life, while the average infant mortality in the city at large was 10.8 per cent. Ustvedt comments that these figures teach nothing new, but they emphasize the vital importance of removing infants at once from a tuberculous environment, and especially from a tuberculous mother.

P. Reckzch[43] says that so important is an early diagnosis of tuberculosis that we must begin in infancy to seek for symptoms and signs of the disease, and continue to seek for them throughout childhood and puberty, if we would prevent the later ravages. Predisposing factors to tuberculosis are found in underfeeding, overwork, and infectious diseases. These factors may act in the parents and through them in the new-born child, even when the parents give no evidence of tuberculosis. The larger the number of relatives in a family who have had tuberculosis, the greater the predisposition of the child. Descendants of tuberculous parents succumb to phthisis more often than descendants of normal parents. They are easy prey to other infections also. In large families it is found that the younger members to whom less of the mother's vitality is given are the commoner victims of tuberculosis. Where there is this predisposition, the children suffer from other infections, as diphtheria, scarlet fever. If both parents have died of tuberculosis, the predisposition of the child is greater than if only one had died of the disease. The nearer the birth of the child comes to the death of the parent, the greater the predisposition and the greater likelihood of death. Children having latent tuberculous infection in the lymphatic system are subject to other infections, especially in the

organs of the respiratory system, and convalescence is slower than in the normal child.

From a study of statistics in Alsace and Lorraine between the years 1905 and 1912, E. Stern[44] has obtained some instructive figures regarding the mortality of tuberculosis in children. The general decrease during this period was 7.5 per cent. In the first year of life this decrease was greatest, due doubtless to the results of infant welfare propaganda; perhaps also to the lowered birth rate which it has been shown existed during this period. In the following period, from 1 to 2 years, the decrease was less marked, 9.6 per cent. In the third year the decrease was 4.8 per cent., and in the period from 3 to 5 years, 8.9 per cent. During the first half of the school years, namely, from 5 to 10 years, the decrease in deaths from tuberculosis was only 4.4 per cent., and Stern thinks this is due for the most part to the influence of school life. The child has new and unaccustomed surroundings, associates with many other children and is compelled to work several hours a day in a closed room. The slightest decrease occurred, however, between the ages of 10 and 15 years, when it was only 2.2 per cent. Puberty here played a very important rôle.

Stern thinks that social workers should take heed of the fact that statistics show a slighter decrease in the mortality from tuberculosis at school age and should institute means of improving home and school hygiene and of giving instruction in personal hygiene, movements which will doubtless result in lowering the mortality statistics for this period. The physician also should do his share in the work.

O. Schlesinger[45] emphasizes the value and harmlessness of the von Pirquet test and the ease with which the reaction is interpreted. He reviews and summarizes reports of the results of this test on hundreds of children and adults in various countries. Analysis of these reports shows that in remote regions having little intercourse with cities, where tuberculosis is always prevalent, the disease has very little foothold. The more the region is visited by people from the cities, the more widespread it becomes. In villages and towns tuberculosis spreads very gradually, probably through the school. In medium-sized cities the children become infected before the school age, while in the large cities a considerable number become infected during the first years of life. Schlesinger comments on the well known fact that tuberculosis takes a much more severe form and a more rapid course among uncivilized than among civilized people, and he believes this is because the latter acquire an immunity through reinfection. He thinks, too, that this acquired immunity explains the lowered mortality from tuberculosis in the last few years in England and Germany.

H. C. Michie,[46] making the von Pirquet test on nearly all children in the Eskimo village on St. Michael's Island, found that 61.5 per cent.

were tuberculous. After a survey of their homes and of the sanitary conditions of the village, he concludes that the environment of these children is such that tuberculosis must increase among them, and that there is a great field for medical missionary work.

J. Rosenberg[47] asks of the medical profession cooperation in furthering the use of immunized milk as a prophylactic measure and remedy for tuberculosis, and impresses the urgent need of facilities and means to produce and supply immunized milk. The author believes in the ultimate control of the great white plague, but not by methods now emphasized, for their inadequacy is proved by the present death rate. The principal cause of failure lies in the fact that the main entrance gate for infection is unguarded. While attacking every possibility of communicating the disease from man to man, the diseased cow is left undisturbed. Cattle tuberculosis is rapidly increasing and is undoubtedly the cause of extensive infection and illness among young children. Rosenberg believes that tuberculosis in cattle can be eradicated by prophylactic injections of bacillary emulsion prepared from dead cultures of both the bovine and human type of tubercle bacilli. This protective vaccination safeguards the healthy cow against infection by her stable companion, and also produces a supply of immunized milk, a remedy for patients infected with tuberculosis. Immunized milk possesses antibacterial qualities like the blood of animals which have been immunized. It is a dilute antitoxic and bactericidal serum. Drinking the milk transmits the antibodies which pass through the intestinal mucous membrane into the general circulation and offer the same immunity as inoculation with antitoxins and antibactericidal serum. The writer reports a number of cases of pulmonary tuberculosis and of tuberculosis of the bones and joints successfully treated with immunized milk. He quotes also the report of Castelli of the University of Genoa, who indorses the claim that protective vaccination secures the cows complete immunity against bovine tuberculosis; that feeding infants immunized milk eliminates the principal source of tuberculosis, and that it is a remedy for every type of tuberculosis.

F. M. Pottenger[48] calls attention to the protective rôle of the lymphatic system against invading bacteria, specially tubercle bacilli. He says that collections of lymphatic tissue, as tonsils, adenoids and Peyer's patches are placed where bacteria are likely to gain entrance to the tissues so that they may be taken up by them and destroyed. He particularly emphasizes the importance of this protective mechanism because of the tendency of ruthlessly sacrificing lymphatic structures in the throat and vault of the pharynx without giving due consideration to their importance. He says he is aware of the fact that tonsils and adenoids must be removed, but he believes that unless they are pro-

ducing distinctly harmful effects they should be left in situ until the child is old enough to have come in contact with pathogenic bacteria in sufficient numbers to have developed a specific cellular defense against them.

TREATMENT

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The following review of L. Jeanneret's[49] book on "Treatment of Medical and Surgical Forms of Tuberculosis" is of especial interest, as heretofore very little mention has been made of the method of treating tuberculosis by intradermal injections of tuberculin.

Following out the idea of Mantoux, Jeanneret uses the intradermal injections of tuberculin as a measure of the patients' specific sensibility and as a therapeutic agent. Subcutaneous injections of tuberculin in infants are useless in determining sensitiveness, because, if the dose is pushed so as to produce a reaction, namely, fever, rapid pulse, loss of weight, and congestion of the tuberculous focus, there is great danger of producing a generalization of the disease. Intradermal injections, on the other hand, cause only a local reaction and are perfectly harmless. Jeanneret observed a febrile reaction in only twenty of 4,000 cases, or 1 per cent., in 200. Moreover, this method is a very simple means of measuring the specific sensitiveness of the patient. All that is necessary is to measure the diameter of the reaction at its height, that is, at the end of forty-eight hours. Jeanneret usually injects as a test, $\frac{1}{10}$ mg., a dose ten times stronger than that recommended by Mantoux. Intradermal injections do not cause any reaction in the non-tuberculous, but in infected persons, whether the process is latent, active or cured, it gives rise to a local reaction, except when the affected individual is cachectic or suffering from acute infectious diseases.

Jeanneret has found that the sensitiveness to intradermal injections varies with the forms and localization of the tuberculous process. Children without manifest symptoms show little sensitiveness to the injections. The reaction averaged 6 mm. in diameter in 800 such

instances. Children with a healed clinical tuberculosis always remain sensitive and the intradermal reaction oscillates around 10 mm. Children with tuberculosis of the tracheobronchial glands are more sensitive and give a reaction 14 mm. in diameter. Children with pulmonary lesions show a hypersensitiveness and an intradermal reaction of around 30 mm. in diameter. In this form the reactions are very irregular. Exacerbations of the disease cause an increase, and amelioration a diminution, in diameter of the reaction. Marked irregularity as well as increase in dimensions of the reaction are of unfavorable prognostic significance. Children with osseous tuberculosis give an intense intradermal reaction of 20 to 30 mm. in diameter. In favorable cases it remains stationary or gradually diminishes until a cure is established. In unfavorable cases it increases in size until just before death, when it disappears. Children with tuberculous pleurisy usually show a marked reaction, 35 to 40 mm., those with tuberculous peritonitis a feeble reaction. Strongest reactions are observed in children with tuberculous polyserositis. In these cases the reaction is often 50 to 60 mm. in diameter. Sensitiveness is also marked in cases of renal tuberculosis. It disappears gradually after extirpation of the diseased kidney. In meningitis and miliary tuberculosis the reaction measures from 15 to 35 mm. and disappears completely just before death.

Jeanneret thinks intradermal injections valuable in the treatment of tuberculosis. He believes that by this method foci are established in the skin from which the tuberculin is gradually absorbed and by which immunity is established. He compares this immunity to that established by absorption of tuberculin from tuberculous glands. Jeanneret uses Koch's old tuberculin for the injections and makes up six solutions diluted so that 1/10 c.c. of each contains 1 mg.; 1/10 mg., 1/100, 1/1,000, 1/10,000 and 1/100,000 mg. of tuberculin. The initial dose for hypersensitive patients is 1/100 mg.; for those less sensitive, 1/10 mg. If the resulting reaction is more than 10 to 15 mm. in diameter, the dose is reduced. If it is less than 3 to 4 mm., the dose is increased. As a rule, an effort is made to maintain a reaction of 5 to 8 mm. The same dose is repeated if the reaction remains this size, the interval between doses being from five to ten days. If the sensitiveness becomes more marked, the interval is increased and diminished again, as the sensitiveness diminishes. The duration of the treatment depends on the clinical condition of the patient; Jeanneret advises it continued even after a cure is established. In unfavorable cases when, in spite of smaller doses, the reaction remains marked without any tendency to diminish, the treatment must be given up.

Jeanneret is very enthusiastic over the results he has obtained with this method of treatment, and he believes tuberculin given in this way

has a curative action even in grave and progressive forms of tuberculosis.

W. W. Howell[50] says treatment of tuberculosis in infancy is essentially the treatment of the primary lesion and preventing the disease from spreading beyond it. The important factors in the treatment are food, fresh air and rest; and these measures must be persisted in long enough to insure good nutrition and a gain in weight. As long as the tuberculosis is kept primary, the infant is safe, but, unless the disease is recognized before the secondary forms develop, little or nothing can be done in the way of treatment.

H. J. Gauvain[51] says it may be stated emphatically that some of the extravagant claims made as to the value of sun treatment of tuberculosis cannot be substantiated. Sunlight alone is not sufficient for the cure of the majority of the severe types; rather it should be regarded as an important, adjuvant treatment, to be employed with care and discrimination. In certain cases its application is without benefit, and is attended by actual danger.

Gauvain summarizes the action of sunlight as follows: On the local lesions it has at first a direct effect. Superficial micro-organisms are destroyed or inhibited by the sterilizing action of the light waves, and this action is assisted by the inflammatory response which results from a reasonable exposure to strong sunlight. Since tuberculosis must be regarded as a general constitutional disease, the more remote effects of sunlight may be reasonably anticipated to be more important in producing its arrest. Remote beneficial effects cannot be obtained without pigmentation of the skin. Pigmentation is not sufficient to produce improvement, but it is a medium through which improvement is obtained. The most marked outward benefit of successful insolation is the extraordinary tonic effects which usually accrue.

The author has formulated a number of rules which must be observed when this treatment is given: 1. The patient's head must always be protected. 2. The patient must never be allowed to become too cold or too hot. 3. On the first day the legs to the knees may be exposed hourly for five minutes. If this is tolerated well, exposure of the knees may last for ten minutes hourly. On the third day exposure of the thighs for ten minutes hourly, and on the fourth day, similar exposure for fifteen minutes may be attempted. On the fifth day exposure of the thighs for fifteen minutes and of the body for five minutes is desirable. On the sixth day exposure of the thighs for fifteen minutes and of the body for ten minutes hourly may be attempted. If the patient is pigmented, the periods of exposure may be gradually increased, until the patient may be completely exposed for periods, and, when pigmentation is fully established, continuous

exposure may be undertaken. 4. Blistering must be carefully avoided. 5. If the temperature exceeds 100 F., the patient should not be exposed the following day, unless special orders are given. 6. Sinuses should be exposed and any purulent discharge from them should be immediately swabbed. 7. A nurse must be on duty during the whole time.

C. N. Dowd[53] draws rather definite conclusions regarding the treatment of tuberculosis of the cervical lymph nodes based on the study of 687 cases, in which the operation was performed by himself or by his associates, and which were kept under observation for twenty-two years. He places his patients in three groups, according to the stage of tuberculous process. In group one are the patients in the early stage of the disease. Tubercle bacilli, he says, are inhaled with the air or swallowed with the food and lodge in the crypts of the tonsils, faucial and pharyngeal. The route of infection from the tonsil to the tonsillar lymph node is a very short one, and the invading tubercle bacilli cause swelling, fibrosis, caseation and possibly abscess formation. If the defense of the gland holds, the process remains local and extends very little beyond the upper group of lymph nodes. Of the 687 patients who form the basis of this paper, 432 were observed in this stage. Ninety-one per cent. of the patients were apparently cured, when last seen, and the writer thinks the results eminently successful.

In group two Dowd places patients with glandular abscesses or sinuses or with enlarged glands extending along the entire jugular chain and along the border of the trapezius muscle. There were 385 patients in this group, and 68.2 per cent. made apparent recoveries. The results obtained in this group were greatly inferior to those in the first, and the writer thinks it would have been much better for these patients to have undergone an operation, while the disease was in its early stage.

In group three are patients showing little power of resistance to tuberculosis. There is involvement of a great number of nodes and usually evidence of tuberculosis in other parts of the body. In this group were fifty patients, and only 35 per cent. were apparently cured. Treatment of this type of cases is far from satisfactory.

Commenting on the subject of tuberculosis of the cervical lymph glands, Dowd says much confusion exists about the term "operation" as applied to these cases. He says that if the incision of an abscess or the removal of a single gland is called an operation, the operative results will be very poor; if the term operation means the removal of all enlarged lymph nodes of the neck, the results will be very good.

In discussing Dowd's paper, J. F. Golden[54] says that tuberculosis of the cervical lymph glands in children has a tendency to cure itself without the aid of surgical intervention. He has found the tuberculin

method the best, together with the administration of fats in the forms of emulsion of cod-liver oil, butter and cream. He has secured by this method a recession of glands, some of them breaking down and discharging a cheesy substance, but uniformly progressing to a cure without enucleation.

R. T. Morris[54] thinks that the majority of cases of tuberculosis of the lymph glands of the neck do not require operation at all, provided that the patient is so situated at hospital or in the private house that he may have full benefit of professional knowledge on the subject. He emphasizes the importance of using tuberculin properly, but believes the best way of dealing with these cases is along the lines of the Bier idea of hyperemia. He has the patient rest the neck against a hot-water bag for several minutes, then an ice-bag, again the hot-water bag for several minutes, then the ice-bag. Morris has also obtained some good results with the Roentgen ray.

W. E. Ladd[54] has for the last four or five years been following the teaching of Dr. Dowd. He has operated in about 160 cases of cervical adenitis, mostly in children. One hundred and thirty of these have been followed for from six months to five years. Of these, 93 per cent. are apparently cured. Ladd emphasizes the importance of removing the tonsil at the same time as the cervical glands. In his series of cases the tonsil was believed to harbor the primary focus in 75 or 80 per cent. of the cases. Ladd believes that if one waits to try tuberculin, hygiene without operation, Roentgen ray and other forms of treatment, a great many cases will progress to tuberculosis which is more disseminated and more difficult to cure.

A. F. Holding[55] has observed the good effects of Roentgen ray on tuberculous glands and is surprised that the method is so little known and seldom advised by the medical profession. The efficacy of the Roentgen-ray treatment on this condition has been demonstrated in surgical clinics and the literature contains reports of 1,500 cases successfully treated. Surgical treatment was orthodox before the discovery of the Roentgen ray, and its therapeutic value is still advised by a large number of physicians. Holding thinks that nonsurgical methods, including Roentgen ray, deep hyperemia and tuberculin should be tried before any patient is submitted to radical operation.

E. Albert-Weil[56] divides tuberculous adenitis into two groups, the inflammatory and the suppurative. The latter he subdivides into closed forms and forms associated with fistulae and cutaneous tuberculosis. He thinks all forms amenable to treatment with the Roentgen ray. In the inflammatory forms the Roentgen ray leads to the disappearance of large masses of glands, but heliotherapy and medical treatment are necessary to combat the tuberculous diathesis and increase the resist-

ance of the patient. In closed suppurative adenitis it is well to evacuate the pus by puncture with a fine needle, as the pus prevents the penetration of the Roentgen ray. In the form with fistula, Weil clears out the fistula and suppurating focus and then applies the Roentgen ray. Weil gives several illustrations of how the enlarged glands recede, even when they are of months' duration.

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